A MULTICENTER, OPEN-LABEL, RANDOMIZED, ACTIVE COMPARATOR STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF LACOSAMIDE IN NEONATES WITH REPEATED ELECTROENCEPHALOGRAPHIC NEONATAL SEIZURES

PROTOCOL SP0968 AMENDMENT 2

PHASE 2/3

Short title:

Study of lacosamide in neonatal seizures

Sponsor:
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 2	11 Feb 2022	Substantial
Amendment 1	13 Oct 2020	Substantial
Original Protocol	25 Mar 2020	Not applicable

Amendment 2 (11 Feb 2022)

Overall Rationale for the Amendment

Changes to the protocol have been made to align the study more closely with the Neonatal Intensive Care Unit's (NICU) standard of care and practice, clarify the age criterion, clarify the Schedule of Activities, align with the current Statistical Analysis Plan (SAP), and align with the current lacosamide (LCM) clinical development program. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 4.1.2 Study periods	Update Baseline Period within the Screening Period from -1 hour to 0 hour to -2 hours to 0 hour.	To align the study more closely with NICU's standard of care and practice.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1.1 Video-EEG 5.1 Inclusion criteria 8.1.1.1 Assessment of seizure burden	Update to reflect the increase in the duration of the Baseline video-EEG recording period from 1 hour to 2 hours. Specify that the occurrence of ENS is to occur during an up to 2-hour period, with at least 30 seconds of cumulative ENS in an hour.	To align the study more closely with NICU's standard of care and practice.
1.3 Schedule of Activities	Reduce the number of ECG assessments to 4 timepoints within the Screening and Treatment Period: Screening or Baseline (-24h to 0h), postdose (1-6h), at 48h, and at 96h. Clarify footnote to specify that the ECG postdose 1-6h is preferred to be taken as close to the first hour as possible.	To align the study more closely with NICU's standard of care and practice.
1.1 Synopsis 2.1 Study rationale 4.2 Scientific rationale for study design 5.1 Inclusion criteria	Update inclusion criteria for age from gestational age to corrected gestational age (CGA), clarify CGA weeks, and	To clarify the age criterion and slightly broaden the potential patient population.

	remove postmenstrual age requirement.	
5.2 Exclusion criteria	Replace exclusion criteria creatinine clearance measured by Schwartz formula with: if participant is in the first 24 hours of life, urine output is <1mL/kg/hour. If older than 24 hours, participant urine output is <1mL/kg/hour or serum creatinine >1.7mg/dL.	To align the study more closely with NICU's standard of care and practice.
1.3 Schedule of Activities	Clarify with a footnote that Treatment Period dosing will be up to the 96 hour timepoint; however, at 96 hours the study participant may enter the Extension period and receive LCM either as oral solution or iv infusion.	The Schedule of Activities indicates that LCM infusion occurs at 96 hours; however, study participants are given the option to receive oral solution or iv infusion at the 96 hour timepoint; therefore, the mark is footnoted to clarify.
1.3 Schedule of Activities	Mark the following assessment: physical and neurological examinations, for conduct at 48 hours of the Treatment Period.	The Schedule of Activities did not indicate physical and neurological examination at 48 hours of the Treatment Period. For consistency with the "Other Endpoints" whereby change from Baseline in physical and neurological examinations is conducted at 24 hours, 48 hours, 72 hours, and 96 hours, the assessment is marked at 48 hours in the Schedule of Activities.
Section 6.3 Measures to minimize bias: Randomization Section 9.1 Definition of analysis sets 9.4 Planned safety analyses Section 9.9 Determination of sample size Section 11 References	Global updates to align protocol with the SAP including alignment of analysis sets and determination of sample size text.	To align with the current SAP for accuracy in the protocol.
1.1 Synopsis 2.1 Study Rationale 2.2 Background 2.2.1 LCM in pediatric studies 2.3 Benefit/Risk Assessment	Global updates of study status and approvals of LCM since last protocol amendment.	To align with the current LCM clinical development program.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**All regions:** +32 238 66561
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A multicenter, open-label, randomized, active comparator study to evaluate the efficacy, safety, and pharmacokinetics of lacosamide in neonates with repeated electroencephalographic neonatal seizures

Short Title:

Study of lacosamide in neonatal seizures

Rationale:

Seizures occur more often during the neonatal period than at any other time during life, the most common cause being hypoxic-ischemic encephalopathy (HIE) as a result of perinatal asphyxia. The current accepted medical practice for neonatal seizures is initial treatment with first-generation anti-epileptic drugs (AEDs) such as phenobarbital (PB) and phenytoin (PHT) with rapid progression to treatment with midazolam (MDZ) for patients without adequate seizure control after 2 doses of PB. Recently, levetiracetam (LEV) is being used more often as first-line and second-line treatment. In up to 50% of patients, seizures are not controlled after first-line treatment with PB or other AEDs, and subsequent treatment with additional AEDs does not significantly improve seizure control. The current available data from randomized, controlled studies to support the choice of AEDs for this indication are limited, and there are currently no definite recommendations on the most suitable treatment. There is a need to investigate which AEDs should be used to treat neonatal seizures and their most appropriate dosages.

Lacosamide (LCM) is approved for treatment of partial-onset seizures for patients ≥4 years of age in the European Union and down to ≥1 month of age in the United States. A study of safety and tolerability of the intravenous (iv) formulation of LCM (EP0060) has recently been completed in pediatric study participants with epilepsy down to the age of 1 month with an infusion duration of 15 to 60 minutes. The efficacy of LCM was evaluated for partial-onset seizures in participants ≥1 month to <4 years of age (SP0967).

SP0968 represents the first clinical study of LCM in neonatal study participants and is designed for the flexible treatment of electroencephalographic neonatal seizures (ENS). This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of LCM in neonates (≥34 weeks of corrected gestational age [CGA], <46 weeks of CGA, and <28 days of postnatal age [PNA]). Lacosamide will be evaluated against an Active Comparator chosen based on the standard of care (StOC) per the local practice and treatment guidelines. Only those participants who do not have adequate seizure control with previous AED treatment (PB, LEV, or MDZ in any combination; additional benzodiazepines [BZDs] are allowed) will be permitted to enroll in SP0968.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of LCM vs an Active Comparator chosen based on StOC in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment	• Reduction in seizure burden measured in the Evaluation [a] video-EEG compared with the Baseline video-EEG
Secondary	
• To further evaluate the efficacy of LCM vs an Active Comparator in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment	• Proportion of responders in the Evaluation [a] video-EEG compared with the Baseline video-EEG • Proportion of participants with at least 80% reduction in seizure burden in the Evaluation [a] video-EEG compared with the Baseline video-EEG • Time to response across the first 48-hours of the Treatment Period compared with the Baseline video-EEG • Time to seizure freedom across the first 48-hours of the Treatment Period compared with the Baseline video-EEG • Absolute reduction in seizure burden across the first 48-hours of the Treatment Period measured by continuous video-EEG compared with the Baseline video-EEG • Percent reduction in seizure burden across the first 48-hours of the Treatment Period measured by continuous video-EEG compared with the Baseline video-EEG • Proportion of responders at the end of the first 48-hours of the Treatment Period • Proportion of study participants who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours after the start of the Treatment Period, categorized by study participants with nonsevere or severe seizure burden at Baseline

Objectives	Endpoints
	• Categorized percentage reduction in seizure burden in the Evaluation [a] video-EEG compared with the Baseline video-EEG (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)
• To evaluate the short-term safety and tolerability of LCM in neonates	• TEAEs as reported by the investigator • Percentage of treatment-emergent marked abnormalities [b] in 12-lead ECG
• To evaluate the PK of LCM in neonates who have seizures that are not adequately controlled with previous AED treatment	• Mean serum concentration of LCM
Other	
• To further evaluate the short-term safety and tolerability of LCM in neonates	• Percentage of treatment-emergent marked abnormalities [b] in hematology and chemistry parameters • Percentage of treatment-emergent marked abnormalities [b] in vital sign measurements (ie, BP and pulse rate) • Change from Baseline in physical and neurological examinations at 24 hours, 48 hours, 72 hours, and 96 hours after the start of initial treatment

AED=anti-epileptic drug; BP=blood pressure; ECG=electrocardiogram; ENS=electroencephalographic neonatal seizures; LCM=lacosamide; PK=pharmacokinetics; StOC=standard of care; TEAE=treatment-emergent adverse event; video-EEG=video-electroencephalogram

[a] The 2-hour evaluation for efficacy will start 1 hour after initiation of randomized treatment (LCM or Active Comparator) and will be used for evaluation of the primary endpoint based on video-EEG.

[b] Marked abnormalities will be defined in the Statistical Analysis Plan.

Overall Design

This is a Phase 2/3, multicenter, open-label, randomized, active comparator study to evaluate the efficacy, safety, and PK of LCM in neonates with repeated ENS compared with an Active Comparator chosen based on StOC per the local practice and treatment guidelines.

Study participants who have confirmation on video-electroencephalogram (video-EEG) of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Treatment Period (ENS is defined as a seizure lasting for at least 10 seconds on video-EEG), despite receiving previous AED treatment (PB, LEV, or MDZ in any combination; additional BZDs are allowed) will be enrolled in the study. Participants must be ≥34 weeks of CGA, <46 weeks of CGA, and <28 days of PNA at the time of signing the informed consent.

The study involves Screening Period of up to 36 hours followed by a 96-hour Treatment Period during which study participants will be randomized 1:1 and stratified by seizure severity to

receive either LCM or an Active Comparator. The Active Comparator treatment will be chosen and dosed based on StOC (per local practice and treatment guidelines). The video-EEG recording needs to have started at least 2 hours before treatment randomization and will continue for 48 hours after administration of the first dose of randomized treatment (LCM or Active Comparator). The 2-hour evaluation for efficacy will start 1 hour after initiation of randomized treatment and will be used for evaluation of the primary endpoint based on video-EEG. Rescue medication, if needed, can be administered during the Treatment Period. Ideally, rescue medication will not be given within the first 3 hours of randomized treatment; however, the administration of rescue medication is always at the discretion of the investigator. At the end of the Treatment Period, study participants may continue to receive randomized treatment in the Extension Period. Study participants who discontinue randomized treatment during the Treatment Period or the Extension Period will enter the Safety Follow-up (SFU) Period. During the SFU Period, study participants randomized to LCM will have the option of down titrating their LCM dose.

A 1:1 (LCM:Active Comparator) randomization scheme will be used for the treatment allocation to participants in the study. Randomization will occur after completion of the End-of-Baseline video-EEG (at least 30 minutes) and after confirmation that the participant has met eligibility criteria. The randomization will be stratified by seizure severity (as defined in Section 8.1.1.1).

Number of Participants

A total of 32 study participants are planned to be enrolled.

Treatment Groups and Duration

The total duration of the study for an individual study participant is a maximum of 42 days and will include the following periods:

- Screening Period: up to 36 hours (-36 hour to 0 hour)
- Treatment Period: 96 hours (0 hour to 96 hour)
- Extension Period: up to 28 days of PNA
- Safety Follow-up Period (with optional down titration): 14 days

During the Treatment Period, study participants will be randomized to either the LCM or Active Comparator (StOC, based on local practice and treatment guidelines) treatment group. Study participants randomized to LCM will receive an iv infusion of LCM over 30 minutes. A dose of LCM 15mg/kg/day is estimated to yield approximately the same plasma concentrations as in an adult receiving LCM 400mg/day. The planned LCM dose in the study may be adjusted during the study as more PK information in neonates is obtained from ongoing studies and as SP0968 progresses. The sponsor will review the interim safety and PK data and inform the investigators if a dose modification is needed. The actual LCM dose during the study for each study participant will be provided by Interactive Response Technology (IRT). Study participants randomized to Active Comparator will receive an Active Comparator treatment chosen and dosed based on StOC (per local practice and treatment guidelines).

Following the Treatment Period, all study participants who remain inpatient and continue to receive the randomized treatment (LCM or Active Comparator) will enter the Extension Period.

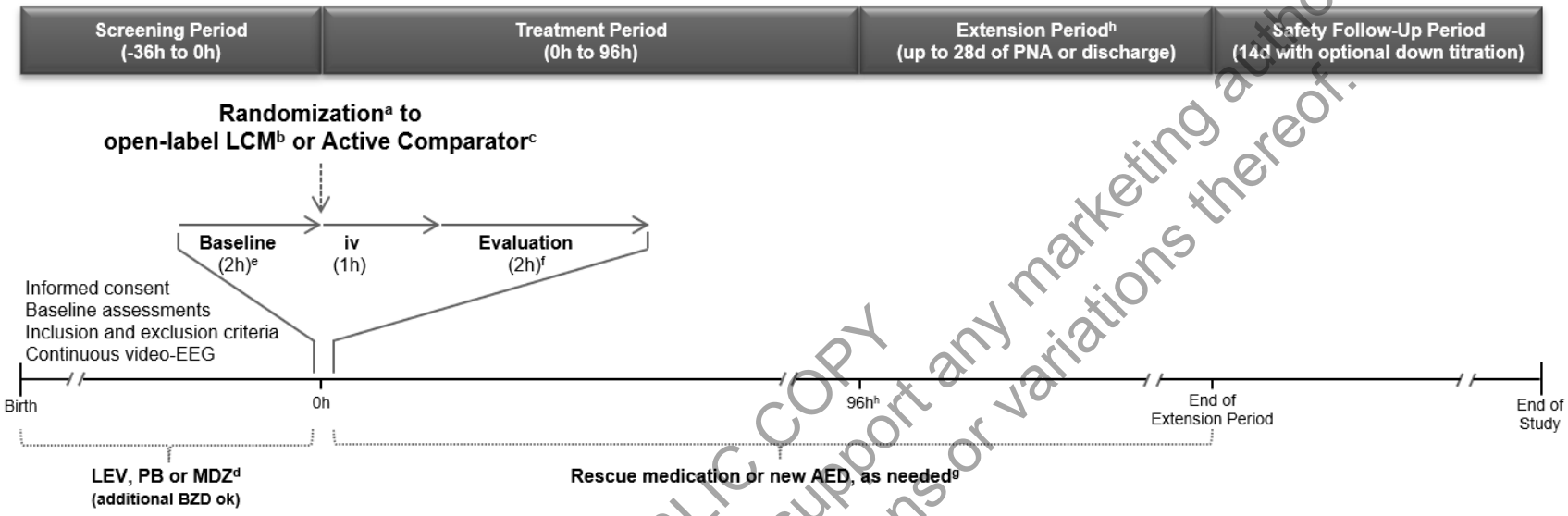
Study participants in the LCM group may continue receiving the same LCM dose administered at the end of the Treatment Period; the LCM dose should not be increased, but may be decreased, at the discretion of the investigator. Participants on LCM should be switched to oral dosing of LCM as soon as medically possible during the Extension Period.

Study participants who discontinue randomized treatment at any time (Treatment or Extension Period), complete the Extension Period, are discharged from the hospital or reach 28 days PNA, will enter the 14-day SFU Period. During the SFU Period, participants on LCM have the option of down titrating their LCM dose over 7 days; it is recommended that the LCM dose be tapered gradually in daily decrements of 3mg/kg/day. Study participants will return to the site for the SFU visit at the end of the 14-day SFU period.

1.2 Schema

A schematic overview of the study design is presented in Figure 1-1.

Figure 1-1: Schematic overview of the study



AED=anti-epileptic drug; BDZ=benzodiazepine; d=day; ENS= electroencephalographic neonatal seizures; h=hour; IRT=Interactive Response Technology; iv=intravenous; LCM=lacosamide; LEV=levetiracetam; MDZ=midazolam; PB=phenobarbital; PNA=postnatal age; SFU=Safety Follow-up; StOC=standard of care; video-EEG=video-electroencephalogram

[a] Study participants eligible based on Baseline video-EEG seizure burden and other inclusion and exclusion criteria will be randomized to the LCM or Active Comparator treatment group.

[b] Study participants randomized to LCM will receive an iv infusion of LCM over 30 minutes, 3 times a day. The actual LCM dose during the study for each study participant will be provided by IRT.

[c] Study participants randomized to Active Comparator will receive an Active Comparator treatment chosen and dosed based on StOC (per local practice and treatment guidelines).

[d] Study participants must have been administered LEV, PB, or MDZ (in any combination) for treatment of ENS prior to enrollment. Other BDZ may have been given additionally. Sodium channel blockers (such as phenytoin or lidocaine) are not permitted prior to enrollment but are permitted in the Active Comparator treatment group (ie, the Active Comparator may be a sodium channel blocker).

[e] Video-EEG recording can be shortened per clinical need (eg, if status epilepticus is detected). If possible, an attempt should be made to record at least 30 minutes of Baseline video-EEG.

[f] Evaluation for efficacy will start 1 hour after initiation of randomized treatment (LCM or Active Comparator) and will be used for assessment of the primary endpoint based on video-EEG.

[g] Ideally, rescue medication will not be given within the first 3 hours of randomized treatment; however, the administration of rescue medication is always at the discretion of the investigator.

[h] Study participants who benefit from randomized treatment (LCM or Active Comparator) can continue to the Extension Period. Study participants who discontinue randomized treatment at any time (Treatment or Extension Period), complete the Extension Period, are discharged from the hospital, or reach 28 days PNA, will enter the 14-day SFU Period with optional down titration. Study participants will return to the site for the SFU visit at the end of the 14-day SFU period.

1.3 Schedule of Activities

The Schedule of Activities during the Screening and Treatment Periods is provided in Table 1-1.
The Schedule of Activities during the Extension and SFU Periods are presented in Table 1-2.

The PK sampling will be performed according to the schedule provided in Table 1-3.

Table 1-1: Schedule of Activities – Screening and Treatment Periods

Assessments	Screening Period [a] Up to 36h: -36h to up to -2h	Screening Period [a] Up to 36h: Baseline Period [b] up to -2h to 0h	Treatment Period 0h to 96h: 0h Evaluation for efficacy [d]	3h Evaluation for efficacy [d]	8h	16h	24h	32h	40h	48h	56h	64h	72h	80h	88h	96h [c]	Early Withdrawal
(Assessment window)	-	-	-	(±15min)	(±60min)												
Informed consent [e]	X																
Inclusion/exclusion criteria	X																
Demographic data	X																
Medical history including Apgar score and Sarnat scale [f]	X																
Vital signs [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical and neurological examinations		X					X			X			X			X	X
Length	X																
Body weight [h]	X						X			X			X			X	X
Head circumference	X [i]																
Primary cause of seizure	X															X [j]	X [j]
ECG [g]	X		X [g]							X [g]						X [g]	

Table 1-1: Schedule of Activities – Screening and Treatment Periods

Assessments	Screening Period [a] Up to 36h: -36h to up to -2h	Screening Period [a] Up to 36h: Baseline Period [b] up to -2h to 0h	Treatment Period 0h to 96h: 0h Evaluation for efficacy [d]	3h Evaluation for efficacy [d]	8h	16h	24h	32h	40h	48h	56h	64h	72h	80h	88h	96h [c]	Early Withdrawal
(Assessment window)	-	-	-	(±15min)	(±60min)												
AED treatment (PB, LEV or MDZ, [additional BZDs allowed])	X [k]	X			X [l]												
Video-EEG [m]	X																
Randomization			X														
LCM infusion			X		X	X	X	X	X	X	X	X	X	X	X	X [n]	
Active Comparator			X [o]														
LCM PK samples [p]			X														
Laboratory assessments (safety) [q]		X					X									X	X
AEs	X																
Concomitant medications	X																
Medical procedures	X																
AEDs [k]	X																

AE=adverse events; AED=antiepileptic drug; BZD=benzodiazepine; ECG=electrocardiogram; ENS=electroencephalographic neonatal seizures; h=hours; HIE=hypoxic-ischemic encephalopathy; ICF=Informed Consent form; IRT=Interactive Response Technology; iv=intravenous; LCM=lacosamide; LEV=levetiracetam; MDZ=midazolam; min=minutes; PB=phenobarbital; PK=pharmacokinetic; SFU=Safety Follow-up; StOC=standard of care; video-EEG=video-electroencephalogram

[a] Screening Period is from signing and dating of the written ICF up to initiation of the first dose of study medication.
[b] The duration of the Baseline video-EEG depends on seizure activity. Study participants with intermittent seizures will enter the Treatment Period based on up to 2 hours of video-EEG recording. Study participants in status epilepticus will enter the Treatment Period based on up to 30min of video-EEG recording, ie, as soon as 15min of continuous seizures or 50% of cumulative seizure activity is confirmed on video-EEG.
[c] If study participants do not benefit from LCM treatment after 96h of LCM administration, LCM administration will be stopped and the participant will be treated per the StOC. Study participants discontinuing LCM treatment during the Treatment Period will enter the SFU Period with optional down titration.
[d] The evaluation for efficacy will start 1h after initiation of randomized treatment (LCM or Active Comparator) and will be used for evaluation of the primary endpoint based on video-EEG.
[e] Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the ICF.
[f] The Sarnat scale will be used to measure the severity of HIE for study participants with HIE.
[g] For study participants in the LCM group only. Electrocardiograms to be taken during the Screening Period (-24h to 0h), postdose (1-6h), at 48h, and at 96h. The ECG postdose 1-6h preferred to be taken as close to the first hour as possible.
[h] Measurement of body weight is optional at 24h, 48h, 72h, and 96h. Dosage of LCM during the Treatment Period will be based on the study participant's weight measured prior to the start of the first LCM administration. However, dosage calculation can be adjusted to a more recent weight measurement, upon discretion of the investigator, if weight is measured during the Treatment Period.
[i] Head circumference Baseline measurement should be taken within 7 days prior to drug administration, or at birth for study participants ≤7 days old.
[j] In case of new information gained since the initial assessment.
[k] The recording of AEDs will include BZDs and opiates taken by the mother at the time of delivery.
[l] Optional for that day.
[m] Video-EEG acquired per StOC prior to consenting and meet the study-specific technical and quality requirements can be used as part of the Baseline assessment video-EEG.
[n] Lacosamide will be administered three times a day, as an iv infusion over 30min. The actual LCM dose during the study for each study participant will be provided by IRT. Treatment Period dosing will be up to the 96h timepoint; however, at 96h the study participant may enter the Extension period and receive LCM either as oral solution or iv infusion.
[o] Standard of care, based on local practice and treatment guidelines.
[p] For participants randomized to LCM treatment, blood microsamples (0.2mL/sample) will be collected following the first LCM infusion and during the Treatment Period. Samples collected at 48, 72 and 96 hours (Days 2, 3 and 4) are optional. Refer to Table 1-3 for further detail on PK sampling times.
[q] For Screening and determination of eligibility, use of laboratory data acquired prior to Screening per StOC inside or outside the study site within 36h prior to the start of the Treatment Period is allowed. For the 24h and 96h assessments, the window is ±12h.

Table 1-2: Schedule of Activities - Extension and Safety Follow-up Periods

	Extension Period	Safety Follow-up Period [a] (with optional down titration)
	Up to 28 days of PNA or withdrawal	14 days (Down titration [b] for 7 days)
Assessments	**q7d**	**Day 14**
(Assessment window)	**(±2 days)**	**(±2 days)**
Vital signs	X	X
Physical and neurological examination	X	X
Biometric parameters: length, body weight and head circumference		X
LCM [c] or Active Comparator administration or dispense [d]	X	
Laboratory assessments (safety) [e]	X	X
AEs	X	X
ECG	X	X
Concomitant medications	X	X
Medical procedures	X	X
AEDs	X	X

AE=adverse event; AED=anti-epileptic drug; ECG=electrocardiogram; IRT=Interactive Response Technology; iv=intravenous; LCM=lacosamide; PNA=postnatal age; q7d=every 7 days; SFU=Safety Follow-up.

[a] All study participants will enter the SFU Period after the Extension Period or if they withdraw from the study at any time. Study participants return to the site for the SFU visit at the end of the 14-day (± 2 days) SFU Period.

[b] Down titration is recommended for study participants in the LCM treatment group who withdraw from the study.

[c] The actual dose of LCM will be provided by IRT.

[d] The study participants in the LCM treatment group must be switched to LCM oral solution as soon as medically possible, and be able to tolerate it. The timing of switching from iv to oral solution in the Extension Period will be at the discretion of the investigator.

[e] Routine safety laboratory assessments performed within 2 days are acceptable. For participants who withdraw, safety laboratory assessments should be performed in a window of ±12 hours.

Table 1-3: Schedule for PK sampling

Assessment	96-hour Treatment Period						
	Day 1				Day 2 [a]	Day 3 [a]	Day 4 [a]
	30 to 90min after start of first infusion	6 to 8h after start of first infusion	30 to 90min after start of second or third infusion	6 to 8h after start of second or third infusion			
LCM PK samples	X	X	X	X	X	X	X

h=hours; LCM=lacosamide; min=minutes; PK=pharmacokinetic

Note: Blood for PK samples should be drawn from a limb different to that of the LCM infusion if using an existing line, or as a subsample of a safety laboratory assessment blood draw, or may be obtained by heel prick. Blood volume per PK sample will not exceed 0.2 mL (use Sarstedt Microvette™ 200 containers with conical inner tube, serum/activator type).

[a] One optional sample per day, preferably obtained shortly before dosing (trough sample) or at any other postdose time point (but never during infusion).

2 INTRODUCTION

Seizures occur more often during the neonatal period than at any other time during life (Volpe, 2008). The most common cause of neonatal seizures is hypoxic-ischemic encephalopathy (HIE) as a result of perinatal asphyxia (van Rooij et al, 2013a). A population-based study suggested that 42% of neonatal seizures were observed following HIE (van Rooij et al, 2013a). Other causes include intracranial hemorrhage and stroke, infections of the central nervous system (CNS), congenital malformations, inborn errors of metabolism, transient metabolic disturbances, maternal drug abuse, or rare neonatal epilepsy syndromes (benign familial neonatal-infantile seizures or fifth-day seizures) (Volpe, 2008; Ronen et al, 1999).

Clinical recognition of seizures in newborns is not always simple due to a highly variable clinical expression (Volpe, 2008; Mizrahi and Kellaway, 1987). As demonstrated by prolonged video-electroencephalogram (video-EEG) recordings, especially following anti-epileptic drug (AED) treatments, electroencephalographic neonatal seizures (ENS) patterns are not always accompanied by clinical signs (Scher et al, 2003; Boylan et al, 2002; Clancy et al, 1988; Mizrahi and Kellaway, 1987).

First-generation AEDs, such as phenobarbital (PB) and phenytoin (PHT), remain the drugs of first (and second) choice because of extensive clinical experience, despite their limited clinical effectiveness and potential neurotoxicity (van Rooij et al, 2013b).

In addition to midazolam (MDZ), other benzodiazepines (BZDs; eg, lorazepam and clonazepam) are used for the treatment of neonatal seizures, often in PB-refractory cases. As one of the most lipophilic BZDs, MDZ readily crosses the blood-brain barrier and provides the advantage of very rapid onset of action. The formation of pharmacologically active (glucuronidated) metabolites of MDZ is considered a disadvantage of MDZ use since drug-drug interactions or renal impairment could cause an undesired accumulation of these metabolites (van Rooij et al, 2013a).

Current treatments for neonatal seizure include PB, PHT, levetiracetam (LEV), lidocaine (LDC), and MDZ (Slaughter et al, 2013).

Neonatal seizures are described in the International League Against Epilepsy report as “subtle because the manifestations are often overlooked.” Most neonatal seizures do not comply with the usual term epilepsy (enduring predisposition to seizures) because they are symptomatic (provoked, reactive) seizures most commonly caused by HIE, cerebral infarction, or infection.

Due to growing evidence that neonatal seizures contribute to an adverse neurodevelopmental outcome, physicians are increasingly focused on the diagnosis and treatment of this condition (Glass et al, 2012). The current available data from randomized, controlled studies to support the choice of AEDs for this indication are limited, and there are currently no definite recommendations on the most suitable treatment (Pressler and Mangum, 2013; van Rooij et al, 2013a). Thus, there is a need to investigate which AEDs should be used to treat neonatal seizures and their most appropriate dosages (Pressler and Mangum, 2013; Glass et al, 2012). Furthermore, although newer AEDs are efficacious for the treatment of seizures in adults and older children, limited progress has been made in the treatment of neonatal seizures (Pressler et al, 2015; Tulloch et al, 2012). Therefore, clinical studies to assess the efficacy and safety of new treatment options in neonates are warranted.

2.1 Study Rationale

Thus far, lacosamide (LCM) is approved for treatment of partial-onset seizures for patients ≥1 month of age in the United States. SP0967 investigated safety, tolerability, and efficacy of LCM in children with epilepsy aged ≥1 month to <4 years of age. SP0967 has been completed with no safety issues identified by safety monitoring and an external Data Monitoring Committee (DMC). Lacosamide is available as tablets, oral solution, and intravenous (iv) formulation. A study of safety and tolerability of the iv formulation has recently been completed in children with epilepsy down to the age of 1 month (EP0060) with an infusion duration of 15 to 60 minutes. Lacosamide was well tolerated in that study and no safety issues were identified.

Lacosamide for the treatment of seizures in the context of chronic epilepsy should be titrated up in weekly steps to reduce CNS and cardiovascular side effects. Acute seizures, such as acute neonatal seizures, require immediate treatment and rapid effective serum levels, which can only be achieved by a loading dose. Safety and tolerability of a loading dose in children has been completed in a retrospective real world evidence (RWE) study that included neonates, and also informed on dosing usage patterns (EP0147).

SP0968 represents the first clinical study of LCM in neonatal study participants, and will evaluate the efficacy, safety, and pharmacokinetics (PK) of LCM in neonates (≥34 weeks of CGA, <46 weeks of CGA, and <28 days of PNA).

2.2 Background

Lacosamide (VIMPAT®, SPM 927, previously referred to as harkoseride, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, or Anticonvulsant Drug Development [ADD] 234037 [used by the National Institutes of Health during the ADD Program]) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates.

Lacosamide belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability (F), and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved worldwide in over 70 countries. In the US, oral tablets, oral solution (syrup), and iv solution of LCM are indicated for the treatment of partial-onset seizures in patients ≥1 month of age.

In the European Union, LCM oral tablets, oral solution (syrup), and solution for iv infusion are indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients ≥4 years of age. The iv formulation at infusion durations of 15 to 60 minutes bid is indicated as an alternative for patients when oral administration is temporarily not feasible.

The oral solution (also referred to as syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution formulations, comparing 2 tablets of LCM 100mg and the oral solution containing LCM 200mg, after single-dose administration in healthy study participants. The PK of LCM and SPM 12809 (major LCM metabolite in humans) in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution.

2.2.1 LCM in pediatric studies

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

Lacosamide is being evaluated in pediatric study participants ≥1 month to 17 years of age with partial-onset seizures in completed and 1 ongoing study. The completed and ongoing pediatric studies are summarized in Table 2-1. Preliminary data have not demonstrated any clinically relevant changes in vital signs, electrocardiograms (ECGs), or clinical laboratory values; or evidence of cardiac-related treatment-related adverse events or body weight changes.

Table 2-1: Overview of ongoing and completed studies of LCM in partial-onset seizures that include study participants <17 years of age

Study number	Study description	LCM dosage (route of administration) [a]	Status
SP847	A Phase 2, multicenter, open-label study to investigate the safety, tolerability, and pharmacokinetics of LCM oral solution (oral solution) as adjunctive therapy in pediatric study participants (≥1 month to ≤17 years of age) with partial-onset seizures	2 to 12mg/kg/day (oral solution)	Complete
SP1047	A Phase 1, multicenter, open-label study to investigate the pharmacokinetics of commercial oral LCM in pediatric study participants (≥1 month to ≤17 years of age) with epilepsy	15mg/mL (oral solution), 50 to 200mg (tablet), or 10mg/mL (oral solution) at the clinically prescribed dose	Complete
SP0969	A Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric study participants (≥4 years to <17 years of age) with partial-onset seizures	6 to 12mg/kg/day (oral solution), 300 to 400mg/day (tablet)	Complete

Table 2-1: Overview of ongoing and completed studies of LCM in partial-onset seizures that include study participants <17 years of age

Study number	Study description	LCM dosage (route of administration) [a]	Status
EP0060	A Phase 2/3 multicenter, open-label study to investigate the safety and tolerability of iv LCM in children (≥1 month to <17 years of age) with epilepsy	If switching from oral to iv: 2 to 12mg/kg/day or 100 to 600mg/day If initiating LCM treatment: For <50kg: 1mg/kg, bid For ≥50kg: 50mg, bid	Complete
SP848	A Phase 2, multicenter, long-term, open-label study to determine safety, tolerability, and efficacy of oral LCM as adjunctive therapy in pediatric study participants (≥1 month to ≤17 years of age) with epilepsy, previously enrolled in SP847, SP0966, or directly enrolled	2 to 12mg/kg/day (oral solution), 100 to 600mg/day (tablet)	Complete
SP0967	A Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric study participants (≥1 month to <4 years of age) with partial-onset seizures	8 to 12mg/kg/day (oral solution)	Complete
EP0034	A Phase 3, multicenter, open-label, extension study to obtain long-term safety and efficacy of LCM oral solution or LCM tablets as adjunctive therapy in pediatric study participants (≥1 month to ≤17 years of age) with partial-onset seizures previously enrolled in SP0967 or SP0969	Up to 12mg/kg/day or 600mg/day	Ongoing

bid=twice daily; iv=intravenous; LCM=lacosamide
[a] Daily dose, unless otherwise specified.

2.3 Benefit/Risk Assessment

Due to growing evidence that neonatal seizures contribute to an adverse neurodevelopmental outcome, physicians are increasingly focused on the diagnosis and treatment of neonatal seizures (Glass et al, 2012). The current available data from randomized, controlled studies to support the choice of AEDs for this indication are limited, and there are currently no definite recommendations on the most suitable treatment option (Ramantani et al, 2019; van Rooij et al, 2013a), and no AED is approved for the treatment of neonatal seizures. First-generation AEDs, such as PB, PHT, and LDC, remain the drugs of first (and second) choice because of extensive clinical experience, despite their limited clinical effectiveness, unpredictable PK, and potential neurotoxicity (van Rooij et al, 2013b). Therefore, studies to assess the PK, efficacy or effectiveness, and safety of new treatment options in neonates are warranted.

Lacosamide has shown efficacy and is approved for use in children ≥1 month of age in the United States. A clinical study in participants with partial-onset seizures from ≥1 month to <4 years of age (SP0967) has been completed and a study of safety and tolerability of LCM iv formulation has recently been completed in children with epilepsy down to the age of 1 month (EP0060); no safety signal has emerged from either study. Moreover, other sodium channel blocking AEDs (such as PHT and LDC) have shown efficacy in the treatment of neonatal seizures (Painter et al, 1999; Boylan et al, 2004) and are included as StOC treatment. Lacosamide, as a sodium channel blocking AED, may be expected to have efficacy. Based on the efficacy in older pediatric population and on the assumed efficacy of other sodium channel blockers in neonatal seizures, LCM will potentially be effective in reducing seizure burden in neonates with seizures that are not adequately controlled with first-line or later-line treatment.

The dosing in SP0968 is based on modeling with data from children ≥1 months of age. Pharmacokinetic analysis is planned on an ongoing basis as study participants are enrolled in SP0968.

There is extensive safety information for LCM across different pediatric age groups and seizure types from different sources. As of Aug 2021, 5778 study participants received LCM while participating in UCB clinical studies for epilepsy including 969 pediatric participants. A clinical study in partial-onset seizures in participants ≥1 month to <4 years of age (SP0967) has been completed. The clinical development program included 141 participants <2 years of age and no safety signal has emerged in that study population. In the UCB Global Safety Database, during the period from 01 Sep 2018 to 31 Aug 2021, 28 initial (4 serious and 24 nonserious) postmarketing cases were reported for participants aged 0 to 1 month. Of the 4 serious cases, 3 cases reported seizure/epilepsy along with drug ineffective/multiple-drug resistance; all involved use of multiple ASMs. Limited information was reported in the remaining 1 serious case with hospitalization. Of the 24 nonserious cases, 23 cases reported no associated clinical events and 1 case reported vomiting that recovered after discontinuation of LCM. An RWE study was completed and provided further information on usage patterns and the safety of loading dose of LCM in children, including neonates (EP0147).

The most relevant known adverse drug reactions (ADRs) of LCM, across all age groups for which LCM is approved, which are expected to be relevant for the neonatal population, are cardiac ADRs (potentially associated with PR interval prolongation or sodium channel modulation), potential for hepatotoxicity, and potential for worsening of seizures. The effect of LCM treatment on the development of a neonate is unknown, but long-term safety information from studies in older children as well as long-term data from pregnancy registries show no evidence of adverse effects on long-term outcome and development.

While the exposure in neonates is still limited, the safety profile of LCM in all other pediatric age groups is acceptable, which is reassuring for the neonate population.

In order to ensure safety during the study conduct of SP0968, continuous safety monitoring will be conducted internally and at intervals through the DMC (Section 9.8). All participants will be under constant surveillance in Neonatal Intensive Care Unit (NICU) with video-EEG monitoring and cardiovascular monitoring as appropriate. Long-term safety will be assessed for participants progressing to long-term safety follow up, when applicable. A safety reporting process is planned to ensure that the UCB study physician and safety physician are informed in real time

about serious adverse events (SAEs) or other AEs deemed important by the investigator for the evaluation of safety.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LCM may be found in the Investigator's Brochure (IB). The current IB reflects the safety profile of LCM as it is known and may change with the accumulation of additional data.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of LCM vs an Active Comparator chosen based on StOC in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment	• Reduction in seizure burden measured in the Evaluation [a] video-EEG compared with the Baseline video-EEG
Secondary	
• To further evaluate the efficacy of LCM vs an Active Comparator in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment	• Proportion of responders in the Evaluation [a] video-EEG compared with the Baseline video-EEG • Proportion of participants with at least 80% reduction in seizure burden in the Evaluation [a] video-EEG compared with the Baseline video-EEG • Time to response across the first 48-hours of the Treatment Period compared with the Baseline video-EEG • Time to seizure freedom across the first 48-hours of the Treatment Period compared with the Baseline video-EEG • Absolute reduction in seizure burden across the first 48-hours of the Treatment Period measured by continuous video-EEG compared with the Baseline video-EEG • Percent reduction in seizure burden across the first 48-hours of the Treatment Period measured by continuous video-EEG compared with the Baseline video-EEG • Proportion of responders at the end of the first 48-hours of the Treatment Period

Objectives	Endpoints
	• Proportion of study participants who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours after the start of the Treatment Period, categorized by study participants with nonsevere or severe seizure burden at Baseline • Categorized percentage reduction in seizure burden in the Evaluation [a] video-EEG compared with the Baseline video-EEG (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)
• To evaluate the short-term safety and tolerability of LCM in neonates	• TEAEs as reported by the investigator • Percentage of treatment-emergent marked abnormalities [b] in 12-lead ECG
• To evaluate the PK of LCM in neonates who have seizures that are not adequately controlled with previous AED treatment	• Mean serum concentration of LCM
Other	
• To further evaluate the short-term safety and tolerability of LCM in neonates	• Percentage of treatment-emergent marked abnormalities [b] in hematology and chemistry parameters • Percentage of treatment-emergent marked abnormalities [b] in vital sign measurements (ie, BP and pulse rate) • Change from Baseline in physical and neurological examination at 24 hours, 48 hours, 72 hours, and 96 hours after the start of initial treatment

AE=adverse event; AED=anti-epileptic drug; BP=blood pressure; ECG=electrocardiogram; ENS=electroencephalographic neonatal seizures; LCM=lacosamide; PK=pharmacokinetics; StOC=standard of care; TEAE=treatment-emergent adverse event; video-EEG=video- electroencephalogram

[a] The 2-hour evaluation for efficacy will start 1 hour after initiation of randomized treatment (LCM or Active Comparator) and will be used for evaluation of the primary endpoint based on video-EEG.

[b] Marked abnormalities will be defined in the Statistical Analysis Plan

4 STUDY DESIGN

4.1 Overall design

SP0968 is a Phase 2/3, multicenter, open-label, randomized, active comparator study to evaluate the efficacy, safety, and PK of LCM in neonates with repeated ENS compared with an Active Comparator chosen based on StOC per the local practice and treatment guidelines. Only those

study participants who do not have adequate seizure control with previous AED treatment will be permitted to enroll in SP0968.

Parent(s) or legal representative(s) will be informed about the study as early as possible and asked to sign the Informed Consent form (ICF). Study participants will then be considered to be enrolled. During the course of the study, parent(s) or legal representative(s) will be updated about the care of their neonate. Parent(s) or legal representative(s) will be informed that they can withdraw their neonate from the study at any time and that this decision will not affect the care of their neonate.

4.1.1 Video-EEG

Video-EEG will be used for the assessment of the study entry criteria and for the assessment of the efficacy endpoints.

Video-EEG recording needs to have started at least 2 hours before treatment randomization and will continue for 48 hours after administration of the first dose of randomized treatment. The video-EEG recording can be shortened per clinical need (eg, if status epilepticus is detected). If justifiable, an attempt should be made to record at least 30 minutes of Baseline video-EEG.

Interruption of the video-EEG is allowed up to 3 hours per day. There should be no interruptions in the video-EEG for the first 3 hours. Depending on medical needs (eg, magnetic resonance imaging to be performed), interruptions longer than this are acceptable. Interpretation of video-EEGs will be done by local readers for care decisions. Start and stop of randomized treatment (LCM or Active Comparator), and the administration of rescue medication will be digitally marked as treatment events on video-EEGs.

The video-EEGs will subsequently be evaluated by a blinded, independent central reader. The independent central reader will be blinded from site-specific information and the study participant's medical history. The video-EEG data should be saved, stored, anonymized, and delivered to the independent central reader in an expeditious manner.

4.1.2 Study periods

The study will consist of the following periods (Figure 1-1):

Screening Period (-36 hour to 0 hour)

The Screening Period will start from the signing and dating of the written ICF and is up to 36 hours prior to the initiation of the first randomized dose of study treatment. During this period, study participants must have been administered StOC treatment (based on local practice and treatment guidelines). These treatments for ENS include LEV, PB, or MDZ (in any combination). Other BDZ may have been given additionally. Sodium channel blockers (such as PHT or LDC) are not permitted prior to enrollment but are allowed as options for the Active Comparator. The previous AED treatments may have been administered at a location other than the study site.

- *Baseline (-2 hours to 0 hour)*

  Baseline is defined as the final 2 hours of the Screening Period. During these 2 hours, study participants will continue to receive the routine care of the NICU and the AED treatment must not be changed. Baseline assessments need to be conducted before randomization including seizure burden assessments (refer to Section 8.1.1.1.1 for details

on seizure burden [severe vs nonsevere] assessment). The interpretation of the Baseline video-EEG should be done immediately before randomization.

Treatment Period (0 hour to 96 hour)

Following the Baseline assessments, study participants will be randomized 1:1 to either LCM or the Active Comparator (based on StOC). The randomization will be stratified by seizure severity.

– *Evaluation (end of 1st hour to the 3rd hour)*

The 2-hour Evaluation will start 1 hour after initiation of randomized treatment (LCM or Active Comparator) and will be used for evaluation of the primary endpoint based on video-EEG.

The Treatment Period will continue through 96 hours or until the decision to stop treatment is made. Rescue medication, if needed, can be administered during the Treatment Period. Ideally, rescue medication will not be given within the first 3 hours of randomized treatment; however, the administration of rescue medication will always be at the discretion of the investigator. For details on rescue medication refer to Section 6.5.3.

For study participants randomized to LCM treatment, LCM will be administered as an iv infusion over 30 minutes. A dose of LCM 15mg/kg/day is estimated to yield approximately the same plasma concentrations as in an adult receiving LCM 400mg/day. The planned LCM dose in the study may be adjusted during the study as more PK information in neonates is obtained from ongoing studies and as SP0968 progresses; thus, participants in this study are planned to be treated at the most appropriate dose, based on evolving cumulative knowledge. The actual LCM dose during the study for each study participant will be provided by Interactive Response Technology (IRT).

The recommendation to adjust the LCM dose will be given by the DMC after review of cumulative PK and safety data. The sponsor will review the data periodically and inform the investigators if dose modification is needed. For details of the safety data review and data monitoring, refer to Section 9.8.

Following the first LCM administration, blood microsamples (0.2mL sample) will be collected during the 96-hour Treatment Period for each study participant for the determination of serum concentrations of LCM, at time points described in Table 1-3. Blood for PK samples should be drawn from a limb different to that of the LCM infusion if using an existing line, or as a subsample of a safety laboratory assessment blood draw, or may be obtained by heel prick.

For study participants randomized to Active Comparator, the Active Comparator treatment will be chosen and dosed based on StOC (per local practice and treatment guidelines).

At the end of the Treatment Period, study participants may continue to receive randomized treatment in the Extension Period. Study participants who discontinue treatment during the Treatment Period will enter the Safety Follow-up (SFU) Period. If study participants do not benefit from LCM treatment after 96 hours of LCM administration, LCM administration will be stopped and the participant will be treated as per StOC.

Study assessments will be performed at the time points outlined in the Schedule of Activities for the Screening and Treatment Periods in Table 1-1. Blood sampling for PK during the Treatment Period will be performed at time points outlined in Table 1-3.

Extension Period (up to 28 days of PNA)

During the Extension Period study participants who remain inpatient have the option to continue to receive the treatment (LCM or Active Comparator) based on their treatment group.

During the Extension Period, study participants in the LCM treatment group may continue receiving the same LCM dose administered at the end of the Treatment Period; the LCM dose should not be increased, but may be decreased, at the discretion of the investigator. Participants should be switched to oral dosing of LCM as soon as medically possible during the Extension Period. Oral dosing of LCM can be three times a day (tid) or bid.

During the Extension Period, study participants in the Active Comparator group will continue to receive the Active Comparator with dosing and route of administration chosen based on the StOC.

Study assessments during the Extension Period will be performed every 7 days, starting from the end of the Treatment Period. Study participants will be hospitalized during this period. The Extension Period covers days and treatments while hospitalized until 28 days of PNA or until the participant is discharged from hospital, whichever occurs first.

At the end of the Extension Period or if discontinuing from the Extension Period, study participants will enter the SFU Period.

Study assessments will be performed at the time points outlined in the Schedule of Activities for the Extension and SFU Periods in Table 1-2.

Safety Follow-up Period (with optional down titration) (14 days)

Study participants who discontinue the randomized study treatment at any time, complete the Extension Period, are discharged from the hospital, or reach 28 days of PNA, will enter the 14-day SFU Period.

For study participants in the LCM treatment group, the SFU Period includes an option to down titrate their LCM dose over 7 days. Down titration is recommended for study participants who discontinue LCM treatment. It is recommended that the LCM dose be tapered in daily decrements of 3mg/kg/day.

Study participants will return to the site for the SFU visit at the end of the 14-day SFU period.

4.2 Scientific rationale for study design

Although newer AEDs are efficacious for the treatment of seizures in adults and older children, limited progress has been made in the treatment of neonatal seizures (Pressler et al, 2015; Pressler and Mangum, 2013; Tulloch et al, 2012). Thus, clinical studies to assess the efficacy and safety of new treatment options in neonates are warranted.

The current accepted medical practice for neonatal seizures is initial treatment with PB with rapid progression to treatment with MDZ, LEV, LDC, or PHT for patients without adequate seizure control after 2 doses of PB. Some clinics start treatment with LEV based largely on its favorable safety profile. In up to 50% of patients, seizures are not controlled after first-line treatment with PB or other AEDs, and subsequent treatment with additional AEDs does not significantly improve seizure control (van Rooij et al, 2013b; Castro Conde et al, 2005; Boylan et al, 2004; Painter et al, 1999). Thus, SP0968 is designed for a flexible treatment of ENS, and only those participants who do not have adequate seizure control with previous AED treatment will be permitted to enroll in the study.

The frequency, voltage, and morphology of the discharges may change within an individual seizure and between seizures in an individual neonate. At enrollment, study participants must be ≥34 weeks of gestationally-corrected age (GCA), <46 weeks of CGA, and <28 days of PNA. Neonates undergoing hypothermia treatment (eg, for the treatment of HIE) will also be enrolled.

4.3 Justification for dose

A pediatric population PK model of LCM (CL0447 Part-IV) was developed using demographic information, dosing records, and LCM plasma concentration measurements, obtained across 6 Phase 2 and Phase 3 studies in children with epilepsy (SP847, SP1047, SP848, SP0969, SP0966, SP0982 pediatric cohort, EP0060, and SP0967). Lacosamide was generally administered orally, except in EP0060 in which participants were dosed iv. Overall, 705 children aged from ≥1 month to <17 years of age, contributed PK information; among them, 95 had been dosed iv in EP0060. The 2 youngest pediatric cohorts, from ≥1 month to <1 year and from ≥1 year to <2 years, numbered 44 and 48 participants, respectively.

A 1-compartment PK model with fixed allometric exponent for distribution volume (Vc) and freely estimated allometric exponent for clearance (CL), and with F implemented on the logit scale, fitted the data well. Incorporating a sigmoid-E_{max} maturation function to the expression of CL resulted in significant improvement. The typical parameter values were: 1.74L/h for CL and 45.4L for Vc (both normalized to 70kg), 0.847 for F, 0.467 for CL allometric exponent, and 1.50 h^{-1} for absorption rate constant (Ka), respectively.

The optimal LCM dosing regimen in newborns is aimed at achieving plasma concentrations in the range of adults dosed at LCM 400mg/day. The reference concentration range was obtained from the main population PK model (CL0447 Part-IV) and was derived from observed PK in 950 adult study participants across Phase 3 studies (SP754, SP755, EP0008, and SP0982).

For extrapolation of the model to newborns, weight and age data were randomly sampled from the National Health and Nutrition Examination Survey database. Simulated dosing in newborns included 5 days of iv dosing followed by oral dosing. Lacosamide plasma half-life was predicted to be significantly shorter in newborns (mean: 7.97 hours; 90% confidence interval [CI]: 7.69 to 8.25 hours) compared with adults (approximately 15 to 16 hours).

The optimal dosing regimen was found to involve initial iv dosing at 5mg/kg tid (or every 8 hours [q8h]) during 5 days, followed by oral dosing at 5mg/kg tid or at 7.5mg/kg bid (or every 12 hours [q12h]) for newborns and infants weighing <6kg. In contrast, optimal dosing for children weighing ≥6kg to <30kg was estimated to be 6mg/kg bid both iv and orally. Of note, given the predicted rapid CL or short half-life of LCM in newborns, simulations indicated that a loading dose was not justified in this population.

The planned LCM dosing in SP0968 is based on the simulations described above and will not involve any dose titration. Since extrapolation from infants to newborns is based on limited amounts of data and may be imprecise due to variability in ontogeny in the metabolic and excretory functions, actual PK measurements conducted in SP0968 will be used to confirm the relationship between LCM dose and serum concentration in neonates.

Furthermore, the posology of LCM is proposed as an approximately 30-minute iv infusion and is supported by PK and safety data available from study participants ≥1 month old (EP0060).

4.4 End of study definition

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1a. Participant must be ≥34 weeks of CGA, <46 weeks of CGA, and <28 days of PNA, at the time of signing the informed consent.

Type of participant and disease characteristics

2a. Participants who have confirmation on video-EEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Treatment Period (ENS is defined as a seizure lasting for at least 10 seconds on video-EEG), despite receiving previous AED treatment for the treatment of electroencephalographic seizures.

The occurrence of ENS during an up to 2-hour period, with at least 30 seconds of cumulative ENS in an hour, must be confirmed by the local video-EEG reader prior to randomized study drug administration. Video-EEG recording can be shortened per clinical need (eg, if status epilepticus is detected). If possible, an attempt should be made to record at least 30 minutes of Baseline video-EEG.

3. Participants must have received either PB, LEV, or MDZ (in any combination) before entering the study.
4. Participants with or without concomitant hypothermia treatment.

Weight

5. Participant weighs at least 2.3kg at the time of enrollment.

Informed consent

6. An Independent Ethics Committee (IEC)-approved written ICF is signed and dated by the participant's parent(s) or legal representative(s).

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Participant with seizures responding to correction of metabolic disturbances (hypoglycemia, hypomagnesemia, or hypocalcemia) or with seizures for which a targeted, known treatment is available.
2. Participant has seizures related to prenatal maternal drug use or drug withdrawal.
3. Participant has known severe disturbance of hemostasis, as assessed by the investigator.
4. Participant has a poor prognosis for survival, as judged by the investigator.
5. Participant has a medical condition that could be expected, in the opinion of the investigator, to interfere with study medication absorption, distribution, metabolism, or excretion.
6. Participant has a clinically relevant ECG abnormality, in the opinion of the investigator (eg, second or third degree heart block at rest or a corrected QT interval [QTc] ≥450ms).
7. Participant has a hemodynamically significant congenital heart disease.
8. Participant has any clinically relevant cardiac arrhythmia.

9a. If participant is in the first 24 hours of life, urine output is <1mL/kg/hour. If older than 24 hours, participant urine output is <1mL/kg/hour or serum creatinine >1.7mg/dL.

Prior/Concomitant therapy

10. Participant receiving treatment with PHT, LDC, or other sodium channel blockers at any time.
11. Participant requires extracorporeal membrane oxygenation.
12. Participant requires or is expected to require phototherapy or exchange transfusion due to elevated bilirubin.

Diagnostic assessments

13. Participant has 2x upper limit of normal (ULN) of any of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), with the following exception:

    For participants with perinatal asphyxia, elevation of AST, ALT, or ALP <5x ULN is acceptable, if initial and peak elevation of liver function tests (LFTs) occur within 5 days after birth, and the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia.

    The determination of ULN will be based on the participant's CGA and the site's normal range values for the respective CGA.

14. Participant has direct (conjugated) bilirubin levels >2mg/dL.

5.3 Lifestyle restrictions

Not applicable.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

If appropriate (in the event of screening failures), rescreening will be allowed for the study. Rescreening for screen-failed study participants will be allowed with prior consultation of the medical monitor, whenever feasible. Once a participant has received at least 1 dose of the study medication or has left the study because a "must withdrawal" criterion is met, rescreening will no longer be possible.

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s) or marketed product(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

A summary of the treatment administered is provided in Table 6-1.

Table 6-1: Treatments administered

Intervention name	LCM		Active Comparator
Dose formulation	iv for infusion [a]	Oral solution [b]	Based on local practice and treatment guidelines
Unit dose strength(s)	10mg/mL		
Dosage level(s) [c]	X [d] mg/kg, tid, infusion over 30 minutes	Y [d] mg/kg, bid, oral	
Route of administration	iv	oral	
Use	Test		Reference
IMP and NIMP	IMP		NIMP
Sourcing	Provided centrally by UCB		Provided by investigational site
Packaging and labeling	Packaged in glass vials	Packaged in amber bottles	Per manufacturer's label
	Clinical drug supplies will be labeled in accordance with the current ICH guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.		

bid=twice daily; GCP=Good Clinical Practice; GMP=Good Manufacturing Practice; ICH=International Council for Harmonisation; IMP=investigational medicinal product; IRT=Interactive Response Technology; iv=intravenous; LCM=lacosamide; NIMP=noninvestigational medicinal product; tid=three times a day

[a] Administered during Treatment Period.

[b] Administered during Extension Period.

[c] For LCM dose, the rounding rules for weight to dose calculations will be provided by IRT.

[d] The actual dose of LCM will be provided by IRT.

6.2 Preparation, handling, storage, and accountability requirements

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

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

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

The investigator (or designee) will instruct the participant's parent(s) or legal representative(s) (in accordance with local regulation) to store the IMP following the instructions on the label

6.2.1 Drug accountability

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

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

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

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

6.3 Measures to minimize bias: Randomization

To reduce the risk of imbalance between treatment groups with respect to seizure burden, randomization will be stratified based on seizure severity. A 1:1 (LCM:Active Comparator) randomization scheme will be used for the treatment allocation to participants in the study. Randomization will occur after completion of the End-of-Baseline video-EEG and after confirmation that the participant has met eligibility criteria.

6.3.1 Procedures for maintaining and breaking the treatment blind

Not applicable; this is an open-label study.

6.4 Treatment compliance

Site personnel who are administering LCM will record information about all doses administered, including the target dose, actual dose administered, and the dates and times of each administration. If the actual dose is less or more than the target dose, the reason a partial or excessive dose was administered will be recorded.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

Concomitant treatment with non-AEDs is permitted at any time throughout the study.

Concomitant treatment with AEDs during the Treatment Period after initiation of randomized treatment is permitted to continue in parallel with the LCM/Active Comparator treatment if study participants are on a stable dose from 1 hour prior to initiation of the LCM/Active Comparator treatment. Changes to concomitant AEDs are permitted from 3 hours onward following first LCM/Active Comparator administration.

Sodium channel blockers are allowed for participants randomized to the Active Comparator treatment group.

For study participants undergoing therapeutic hypothermia treatment, the target low body temperature achieved and age since birth when cooling began will be recorded. Rewarming of study participants will be documented in the same way.

6.5.2 Prohibited concomitant treatments (medications and therapies)

Use of anti-arrhythmia medications is prohibited during LCM administration.

Sodium channel blockers are prohibited for participants randomized to the LCM treatment group.

6.5.3 Rescue medication

Any treatment initiation with a new AED, or any increase of dose or frequency of an existing concomitant AED for the treatment of seizures during the Treatment Period is considered rescue treatment. Rescue medication can be given at any time if considered necessary by the investigator.

However, during the Treatment Period rescue medication should not be administered, if possible, in the following time frames:

- During the first 3 hours after the initial dose of LCM/Active Comparator. If this occurs, participants will be considered nonresponders for the evaluation of the main efficacy variable.

Rescue medication should be given if the following occurs:

- There is no improvement in seizure burden within the first 3 hours after administration of LCM/Active Comparator.
- Seizure burden is unacceptable to the investigator, in which case rescue medication can be given earlier at any time, but ideally not in the first 3 hours after the initial administration of LCM/Active Comparator.

6.6 Dose modification

For participants in the Active Comparator treatment group, local treatment guidance will be followed if any dose modification is necessary.

For participants in the LCM treatment group, the dose of LCM can be reduced based on clinical judgement of the investigator after the first dose.

6.7 Criteria for study hold or dosing stoppage

Serious adverse events and AEs of special interest will be monitored and triaged by the study physician and UCB Patient Safety (PS) in real time. After triage, events will be passed on to the DMC as appropriate. The DMC or sponsor can convene an ad hoc DMC meeting to review the data and make recommendations on the continuation or modification of the study. The objectives and procedures for the DMC will be detailed in the DMC Charter.

UCB will take appropriate action based on DMC recommendation.

Detailed procedures for reporting SAEs and other safety events which may meet study hold criteria are provided in Appendix 7 (Section 10.8).

6.8 Treatment after the end of the study

Study participants who remain inpatient and who benefit from the LCM treatment may continue LCM if able to switch to oral LCM in the Extension Period. Continuation of LCM after the study is at the discretion of the treating physician based on the best interest of the participant. Lacosamide may be obtained by an expanded access program, if permitted by the local regulatory authority, or as commercial product if available/approved.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

7.1.1 Liver stopping criteria - potential drug-induced liver injury

Study participants 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:

1. Study participant has direct (conjugated) bilirubin levels >2mg/dL.
2. Study participant has AST, ALT, or ALP values 3x ULN, with the following exception:

   For participants with perinatal asphyxia, elevation of AST, ALT, or ALP <5x ULN is acceptable for continuation in the study, if initial and peak elevation of LFTs occur within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within a few days after birth, and subsequent normalization until up to Day 14 after birth).

   In case AST, ALT, or ALP elevation ≥5x ULN occurs within 5 days after birth, study drug must be discontinued and LFTs retested within 24 hours.

   The determination of ULN will be based on the study participant's CGA and the site's normal range values for the respective CGA.
3. Study participant requires or is expected to require phototherapy or exchange transfusion due to elevation of total bilirubin values.

Specific assessments and follow-up actions for PDILI are provided in Appendix 6 (Section 10.6).

7.1.2 ECG stopping criteria

Electrocardiograms will be reviewed locally by the investigator or a qualified designee. If the reading identifies second or third degree atrioventricular (AV) block, a QTc ≥500ms, or another abnormal ECG finding that is assessed by the investigator to be clinically significant, then the study participant must be withdrawn from the study.

Any new clinically relevant finding should be reported as an AE.

7.1.3 Temporary discontinuation

Temporary discontinuation of LCM is not allowed in this study.

7.1.4 Rechallenge

Rechallenge with LCM is not allowed in this study.

7.2 Participant discontinuation/withdrawal from the study

Parent(s) or legal representative(s) are free to withdraw the participants from the study at any time, without prejudice to their continued care.

Study participants **must** be withdrawn from the study if any of the following occur:

1. The sponsor or a regulatory agency requests withdrawal of the study participant.
2. Parent(s) or legal representative(s) withdraw their consent for the study participant to participate.
3. Study participant requires phototherapy or exchange transfusion due to elevation of total bilirubin.
4. Study participant has QTc interval of ≥500ms that is confirmed by a cardiologist over-read on any ECG.
5. Study participant develops a second or third degree AV block.

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

1. Study participant experiences prolongation of seizure duration, a worsening of seizure burden, or emergence of a new seizure type considered by the investigator to require intervention.
2. Investigator may withdraw study participant due to any medical condition, based on clinical judgment and discretion.
3. Study participant requires a medication that is not permitted by the protocol.
4. Study participant has AST, ALT, or ALP values between >2x and ≤3x ULN, with the following exception:

   For study participants with perinatal asphyxia, elevation of AST, ALT, or ALP <5x ULN is acceptable for continuation in the study, if initial and peak LFT elevation occur within 5 days after birth, and if the time course of LFT elevation is compatible with hepatic injury due to perinatal asphyxia (ie, peak LFT elevation within a few days after birth, and subsequent normalization until up to Day 14 after birth).

The determinations of ULN will be based on the study participant's CGA and the site's normal range values for the respective CGA.

5. Study participant has rapidly increasing total bilirubin without requiring or being expected to require phototherapy or exchange transfusion; the participant's withdrawal will be at the discretion of the investigator.

Investigators should attempt to obtain information on participants in the case of withdrawal. The investigator should document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The electronic Case Report form (eCRF) must document the primary reason for withdrawal.

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

7.3 Lost to follow up

During the Extension Period, a participant will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and the participant's parent(s) or legal representative(s) is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant's parent(s) or legal representative(s) and reschedule the missed visit as soon as possible and counsel the participant's parent(s) or legal representative(s) on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant's parent(s) or legal representative(s) (at least 1 phone call and 1 written message to the participant's parent[s] or legal representative[s]), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant's parent(s) or legal representative(s) continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of lost to follow up documented in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedules of Activities (Table 1-1 and Table 1-2).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the Schedules of Activities (Table 1-1 and Table 1-2).

8.1.1 Assessments of primary efficacy endpoints

8.1.1.1 Assessment of seizure burden

For this study, an ENS is defined as an EEG seizure lasting for at least 10 seconds on video-EEG. Baseline seizure burden is defined as seizure burden measured on the continuous video-EEG (total ENS in minutes per hour) during a period of up to 2 hours immediately prior to the first administration of study drug.

8.1.1.1.1 Categorization of seizure burden severity by the investigator

Categorization of seizure burden into severe vs nonsevere seizure burden will be used both for stratification across the 2 treatment groups as well as for responder criteria.

For the categorization into severe vs nonsevere seizure burden, the investigator will evaluate the Baseline video-EEG. A participant is categorized as having severe seizure burden if there is any 30-minute period of more than 50% seizure burden in the Baseline video-EEG, and as having nonsevere seizure burden otherwise.

8.1.1.2 Assessment of responder

Seizure burden assessment will be based on the interpretations of the central reader.

A responder is defined as a study participant who achieved the following reduction in seizure burden (Section 8.1.1.1) without need for rescue medication, compared with the seizure burden measured during the Baseline Period immediately prior to IMP administration, evaluated for a 2-hour period starting 1 hour after the start of initial treatment:

- At least 80% reduction of seizure burden in participants who were categorized as having nonsevere seizure burden during Baseline

  OR

- At least 50% reduction of seizure burden in participants who had at least one 30-minute period of severe seizure burden during Baseline

For the analysis of the efficacy endpoints, study participants will be considered nonresponders if any of the conditions below occurred after initiation of treatment:

- Participant started another AED

- Participant increased the dose or frequency of administration of an AED ongoing at the time the first LCM or Active Comparator infusion started (maintenance dose of ongoing AED to keep target levels will be allowed)
- Participant switched to another AED
- Participant was administered any single dose rescue medication (eg, a BZD) for the treatment of ENS

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedules of Activities (Table 1-1 and Table 1-2).

8.2.1 Medical history including Apgar score

The Apgar score describes the condition of the newborn infant immediately after birth (Papile, 2001) and, when properly applied, is a tool for standardized assessment. It also provides a mechanism to record fetal-to-neonatal transition. Apgar score is collected routinely at birth and the data will be used as part of the medical history for the study participant.

The Apgar score comprises 5 components: heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0, 1, or 2. The score is reported at 1, 5, and 10 minutes after birth. The Apgar score continues to provide convenient shorthand for reporting the status of the newborn infant and the response to resuscitation (Committee on Obstetric Practice, ACOG; American Academy of Pediatrics; Committee on Fetus and Newborn, ACOG, 2006).

8.2.2 Vital signs

Vital sign measurements, including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation (pulse oximetry), and body temperature, will be measured.

8.2.3 Physical and neurological examinations

Physical and neurological examinations will be performed by a medically qualified clinician. The physical examinations will include a check for the presence of skin rash and skin hypersensitivity.

Clinically significant new or worsened abnormalities must be reported as AEs.

8.2.3.1 Sarnat score

Physical and neurological assessments for study participants with HIE will also include the Sarnat scale, a classification scale for HIE with grading based on clinical presentation, EEG findings, the presence of seizures, and the duration of illness. The Sarnat grading scale comprises 6 components: alertness, muscle tone, seizures, pupils, respiration, and duration assessed together to provide 3 stages (Grade I [mild]; Grade II [moderate]; Grade III [severe]) of HIE (Sarnat and Sarnat, 1976).

8.2.4 Biometric parameters

Biometric parameters, including length, body weight, and head circumference, will be measured. The Baseline head circumference measurement should be taken within 7 days prior to drug administration, or at birth for study participants ≤7 days old.

8.2.5 Electrocardiograms

Standard 12-lead ECGs will be performed. Care should be taken to assure proper lead placement and quality ECG recordings.

8.2.6 Total blood collected

Per guidance (Food and Drug Administration [FDA] Draft Guidance, July 2019), total blood loss during the study, per day, and overall, due to safety laboratory determinations, PK determinations, and any other blood loss including during maneuvers must be estimated and should be less than the maximum limit.

Total blood volume (TBV) in a newborn is 85mL/kg.

Total blood loss should not exceed 1% to 5% of TBV in 24 hours, and should additionally not exceed 3% to 10% of TBV in a month (unless local Institutional Review Boards [IRBs] have stricter rules). The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 17mL.

8.2.7 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedules of Activities (Table 1-1 and Table 1-2) for the timing and frequency.

Laboratory measurements, including laboratory assessments for PDILI, will be performed by local laboratories unless historical data are available. Historical safety laboratory assessments, previously collected as StOC, may be accepted from referring hospitals as Baseline measurement if performed within 36 hours prior to the Treatment Period.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Schedules of Activities (Table 1-1 and Table 1-2).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

Markedly abnormal laboratory values will be defined in the SAP.

8.3 Adverse events and serious adverse events

The definitions of AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by a caregiver, surrogate, investigator or designee, or the participant's legally authorized representative.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that cause the participant to discontinue the IMP (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the time of informed consent at the time points specified in the Schedules of Activities (Table 1-1 and Table 1-2). The participant will be monitored for AEs from the time of enrollment (consent). If the participant does not meet the study eligibility criteria, then the participant will be a screen failure. Adverse events leading to screen failure will not be counted in the study analyses.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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 14 days from the end of the study for each participant, and to also inform the participant's parent(s) or legal representative(s) of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the caregiver is the preferred method to inquire about AE occurrences.

8.3.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and nonserious AEs of special interest (as defined in Section 8.3.5), will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.4.1 Immediate reporting of AEs

The following AEs must be reported immediately:

- Serious adverse event:
  - Adverse event that the investigator classifies as serious by the definitions of SAE (Section 10.3) regardless of causality
  - New onset or worsening of status epilepticus after the administration of LCM
- Infantile spasms
- Suspected transmission of an infectious agent via a medicinal product
- Adverse event of special interest (Section 8.3.5)

8.3.5 Adverse events of special interest

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

The following are LCM's 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 (<95bpm; Fleming et al, 2011).
- Serious suspected multi-organ hypersensitivity reactions

  Serious suspected multi-organ hypersensitivity cases may be identified and reported to the sponsor by the investigator using the following algorithm as agreed with the US FDA.

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

  Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
    - Eosinophils % ≥10%

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

- 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 be reported if an alternative etiology is identified during investigation and monitoring of the participant.

8.4 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 study medication so that investigators, clinical study participants, 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 UCB PS representative. The DMC will be informed of the emerging safety issue and safety signals.

As appropriate for the stage of development and accumulated experience with the study medication, 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.

8.5 Treatment of overdose

Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE.

For this study, the combined LCM dose per day should not exceed 22mg/kg.

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and ECG and laboratory abnormalities until return to normal and for at least 3 days.
3. Obtain a serum sample for LCM PK analysis within 3 days from the date of the last dose of LCM if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

8.6.1 Pharmacokinetic sampling and handling

The time points for the collection of PK samples during the Treatment Period are described in Table 1-3.

For the determination of serum concentrations of LCM, up to 7 blood microsamples (0.2mL sample) will be collected per study participant. Blood samples should be collected in Sarstedt Microvette 200 containers with conical inner tube, serum type with coagulation activator. Pharmacokinetic samples will be obtained either through a venous or arterial catheter or taken from routinely performed heel pricks. Blood for PK samples should be drawn from a limb different to that of the LCM infusion.

Additional opportunistic blood samples for the PK analysis (Leroux et al, 2015) may be obtained at the investigator's discretion at any time during the Treatment Period. As opportunistic blood samples will be taken from routine laboratory blood samples, they are not considered an additional burden for the neonates. The plan for microsampling in SP0968 is consistent with blood sampling schema in other neonatal studies (Allegaert and van den Anker, 2015; Jullien et al, 2015; O'Hara et al, 2015; Zhao and Jacqz-Aigrain, 2015; Zhao et al, 2014).

Exact dosing and sampling times will be recorded in the eCRF.

The analysis of PK samples will be performed by liquid chromatography with tandem mass spectrometry at a central laboratory.

8.6.2 Pharmacokinetic sample shipment

Instructions on blood sample collection, processing, storage, and labeling/shipping will be provided in the Laboratory Manual for this study. Appropriate storage and shipping temperatures will also be stated in the Laboratory Manual.

8.6.3 Pharmacokinetic analysis

Measured concentrations will be introduced in the existing pediatric population PK model. After finalization of the study, the existing population PK model for LCM will be updated with the measured concentrations to further optimize the dose recommendations for LCM.

8.7 Genetics

Genetics will not evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters will not evaluated in this study.

8.9 Biomarkers

Collection of samples for other biomarker research is not part of this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the SAP. In general, descriptive summaries will be used to present the study results by treatment groups.

9.1 Definition of analysis sets

Analysis sets will be defined as follows:

- The All Participants Screened Set will consist of all study participants with a signed completed ICF as reported on the eCRF.
- The Safety Set (SS) will consist of all enrolled study participants who take at least 1 dose of the randomized treatment. All safety analyses will be performed on the SS.
- The Full Analysis Set (FAS) will consist of all study participants in the SS who have a minimum of 30 minutes of interpretable video-EEG data from both the Baseline and the first 3 hours after randomization to the initial study medication treatment The primary analysis set for the efficacy data will be the FAS.
- Per-Protocol Set (PPS) will include all participants in the FAS who did not have important protocol deviations related to efficacy. The secondary analysis set for the efficacy data will be the PPS.
- The Pharmacokinetic Per-Protocol Set will consist of all study participants who provide at least 1 measurable serum sample (with recorded sampling time) on at least 1 post-Baseline Visit with documented study drug intake times.

9.2 General statistical considerations

All statistical computations will be performed using SAS® version 9.4 or higher (SAS Institute, NC, USA).

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

9.3 Planned efficacy analyses

9.3.1 Analysis of the primary efficacy endpoint

The primary efficacy endpoint (reduction in seizure burden measured in the Evaluation video-EEG compared with the Baseline video-EEG; “Evaluation” is the 2-hour evaluation for efficacy that will start 1 hour after initiation of randomized treatment [LCM or Active Comparator]) will be analyzed using the Bayesian methodology at the end of the study. This will involve utilizing a linear model with treatment, severity, and Baseline seizure burden as variables and assuming normally-distributed errors. The prior distribution is vague (normal prior distribution with zero mean and large variance for the coefficients of the variables in the model and a gamma prior with a large tail for the variance of the data). The posterior distribution for each coefficient and for the difference between LCM and Active Comparator will be summarized (using means, SD, 90% credible intervals, and other summary statistics as needed).

The posterior probability that the difference (LCM-Active Comparator) in seizure burden is negative (ie, the probability that LCM is better than Active Comparator) will be presented. Other clinical factors that are deemed clinically important (eg, age) will be detailed in the SAP and will be used for a sensitivity analysis.

Video-EEGs will be assessed locally by the investigator for any medical decisions or medical interventions. The final analysis of video-EEG outputs will be based solely on the assessment of a central reader. All efficacy variables will be analyzed by the primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes) and concomitant use of hypothermia, and reported for each study participant using data listings.

9.3.2 Analysis of the secondary efficacy endpoints

All secondary endpoints, listed below, will be summarized descriptively.

- Proportion of responders in the Evaluation [a] video-EEG compared with the Baseline video-EEG
- Proportion of participants with at least 80% reduction in the Evaluation [a] video-EEG compared with the Baseline video-EEG
- Time to response across the first 48-hours of the Treatment Period
- Time to seizure freedom across the first 48-hours of the Treatment Period
- Categorized percentage reduction in seizure burden in the Evaluation [a] video-EEG compared with the Baseline video-EEG (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)
- Absolute reduction in seizure burden across the first 48-hours of the Treatment Period
- Percent reduction in seizure burden across the first 48-hours of the Treatment Period
- Proportion of responders at the end of the first 48-hours of the Treatment Period
- Proportion of study participants who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours after the start of the Treatment Period, categorized by study participants with nonsevere or severe seizure burden at Baseline

[a] The 2-hour evaluation for efficacy will start 1 hour after initiation of randomized treatment (LCM or Active Comparator) and will be used for evaluation of the primary endpoint based on video-EEG.

9.3.2.1 Time to response

Median time (in hours) to the 50% reduction in study participants with severe seizure burden or 80% reduction in study participants with nonsevere seizure burden and the corresponding 95% CIs will be provided based on Kaplan-Meier estimation across the first 48-hours of the Treatment Period. The 95% CI will be provided for descriptive purposes only.

9.3.2.2 Time to seizure freedom

Median time (in hours) to seizure freedom and the corresponding 95% CIs will be provided based on Kaplan-Meier estimation across the first 48-hours of the Treatment Period. The 95% CI will be provided for descriptive purposes only.

9.4 Planned safety analyses

Descriptive summaries will be presented by the treatment groups for AEs, SAEs, physical and neurological examinations, laboratory results, heart rate, vital signs, body weight, and head circumference. Study participant characteristics related to safety, such as cooling status variables (target low body temperature, age since birth when cooling began, duration of cooling [date and start and stop time of cooling]), rewarming status variables (duration of rewarming [date and start and stop time of rewarming]), and the mother's use of AEDs (including BZD and opiates) at childbirth will be listed. The primary cause of seizure (eg, HIE, hemorrhage, or infarction; CNS malformations; CNS infections; undetermined causes) will also be used to categorize the safety review.

9.5 Planned pharmacokinetics analyses

Summary descriptive statistics of serum concentrations will be derived per time point.

Serum concentrations of LCM, together with demographic and other variables, will be introduced in the existing population PK model. The model will be used for simulating various dosing regimens to establish dosing recommendations as a function of developmental variables. The population PK analysis will be reported separately.

9.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the key efficacy, safety, and PK outcomes for an individual study participant. 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.

9.7 Handling of dropouts or missing data

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

9.8 Planned interim analysis and data monitoring

No formal interim analysis for determination of futility or efficacy is planned for this study. To ensure study participant safety, periodic reviews of safety data will be performed using the DMC. Serious adverse events and other significant events will be monitored and triaged by the medical monitor and UCB PS in real time. After triage, events will be passed on to the DMC as appropriate. In addition, 3 reviews of safety and PK data by the DMC are planned when 25%, 50%, and 75% of study participants have been randomized, completed, and have data available for evaluation, and at study completion. The objective, procedures, and timing of DMC safety assessments to evaluate risk and benefit for study participants in SP0968 will be described in the DMC Charter.

9.8.1 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 9.8. A recommendation for stopping should be based on the collective experience of the DMC members. After meeting to review data from each treatment group, 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.

9.9 Determination of sample size

Randomized, controlled studies in neonatal seizures are rare, have usually been conducted with small to modest samples sizes and have almost exclusively focused on first-line treatment of neonatal seizures, usually comparing the historical standard of PB to a new intervention, typically either LEV or a sodium channel blocking agent such as PHT. Two major studies in first-line treatment of neonatal seizures have shown enormous differences in responder rates to PB vs LEV (80% vs 23%; NEOLEV-2 study, Sharpe et al, 2020) and to PB vs PHT (72.2% vs 14.5%; Pathak et al, 2013) although other studies have shown smaller or no differences in studies with similar designs (Painter et al, 1999, Gowda et al, 2019). Only 1 randomized controlled study comparing different AEDs in the second-line treatment of neonatal seizures has ever been published (Boylan et al, 2004). In that study, 11 participants were randomized to receive either the sodium channel blocker lignocaine or a BZD. None of the 6 neonates on either of the 2 BZDs responded, but 3 of the 5 neonates on lignocaine did.

Given the scarcity of prior evidence in randomized controlled studies in the chosen indication and line of treatment, this study should be considered exploratory with no formal sample size calculation. The chosen sample size of 32 is able to detect a treatment difference of 25% in the response rate with a power of 75%.

The relationship of the efficacy metric (difference in means between the two treatment groups) with the related, more interpretable metric (response rate) is presented in Table 9–1.

Table 9–1: Example of assumed responses for the two treatment groups and treatment effects using different metrics

Response Assumption Scenario	Difference in means (log(x+1))	Modelled difference in proportions (assuming Active Comparator Response Rate (RR) = 20%)
1	-0.82	35%
2	-0.7	30%
3	-0.6	24%

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, ICF, IB, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-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 participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

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 participants. 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 participant 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.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the investigator and/or contract research organization agreements, as applicable.

10.1.3 Informed consent process

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 participant's parent(s) or legal representative(s) in both oral and written form by the investigator (or designee). Study participant's parent(s) or legal representative(s) will have the opportunity to discuss the study and its alternatives with the investigator.

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

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

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

The participant's parent(s) or legal representative(s) may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when his/her parent(s) or legal representative(s) has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained written consent from the participant's parent(s) or legal representative(s) to participate in the study.

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant 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 participant'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 participant's study participation, and autopsy reports for deaths occurring during the study).

The participant's parent(s) or legal representative(s) must be informed that participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s) or legal representative(s).

The participant's parent(s) or legal representative(s) must be informed that participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Data quality assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the investigator for the minimum retention period mandatory under the applicable local laws and regulations. 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.

Quality tolerance limits will be established for the study using parameters related to PS reporting and reliability of study results. The parameters will be monitored throughout the study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.5.1 Case Report form completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

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

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

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

10.1.5.2 Apps

No Apps will be used in this study.

10.1.6 Source documents

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

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, quality of life

questionnaires, or video, 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 participant's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

10.1.7 Study and site closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study medication development

10.1.8 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Protocol-required safety laboratory assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
The results of each test must be entered into the eCRF.				

NOTES :

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6. All events of ALT ≥3× upper limit of normal (ULN) and bilirubin ≥2× ULN (>35% direct bilirubin) or ALT ≥3× ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

- Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and follow up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Regulatory Authorities. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Regulatory Authorities.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the investigator must be mild, moderate, or severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The investigator will also consult the investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to SAE coordinator] by telephone.
- Contacts for SAE reporting can be found in Serious Adverse Event Reporting section at the front of the protocol.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Not applicable.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – Suggested actions and follow-up assessments

Participants with PDILI must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants 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 study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB study physician and the investigator for study participants who have ALT >5x ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver chemistry stopping criteria	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin [a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR [b]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT ≥3xULN and cannot be monitored weekly for 4 weeks
Symptomatic [c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested actions and follow-up assessments	
Actions	**Follow-up assessments**
• **Immediately** discontinue study medication. • Report the event to the sponsor **within 24 hours.** • Complete the liver event electronic Case Report form (eCRF), and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE. [b] • Perform liver chemistry follow-up assessments.	• Viral hepatitis serology [d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis 60 minutes after the most recent dose [e] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)

Liver chemistry stopping criteria	
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study medication unless allowed per protocol and sponsor approval is granted • If restart/rechallenge is **not allowed per protocol or not granted**, permanently discontinue study medication and continue the participant in the study for any protocol-specified follow-up assessmentsConsider the need for a toxicology screening **MONITORING:** **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. **<u>If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline.	• Fractionate bilirubin, if total bilirubin ≥2x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury or hypersensitivity, on the adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3x ULN **and** bilirubin ≥2x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3x ULN **and** bilirubin ≥2x ULN (>35% direct bilirubin) or ALT ≥3x ULN and INR >1.5 may indicate severe liver injury **(possible "Hy's Law") and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

[d] Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] PK sample may not be required for participants known to be receiving Active Comparator treatment. Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's caregiver's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the study Laboratory Manual.

10.7 Appendix 7: Medical device adverse events, adverse device effects, serious adverse events and device deficiencies: definition and procedures for recording, evaluating, follow up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

The **investigator must notify the study sponsor as soon as possible** (within 24 hours of becoming aware of the event) by contacting the SAE Reporting info at the beginning at the protocol.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

ADD	Anticonvulsant Drug Development
ADR	adverse drug reaction
AE	adverse event
AED	anti-epileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
bid	twice daily
BZD	benzodiazepine
CI	confidence interval
CL	clearance
CNS	central nervous system
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
ENS	electroencephalographic neonatal seizures
F	bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
CGA	corrected gestational age
GCP	Good Clinical Practice
HIE	hypoxic-ischemic encephalopathy
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
iv	intravenous(ly)

LCM	lacosamide
LDC	lidocaine
LEV	levetiracetam
LFT	liver function test
MDZ	midazolam
NICU	Neonatal Intensive Care Unit
PB	phenobarbital
PDILI	potential drug-induced liver injury
PHT	phenytoin
PK	pharmacokinetic(s)
PNA	postnatal age
PPS	Per-Protocol Set
PS	Patient Safety
QTc	corrected QT interval
qxh	every x hours
RWE	real world evidence
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SFU	Safety Follow-up
SS	Safety Set
StOC	standard of care
tid	three times a day
TBV	total blood volume
ULN	upper limit of normal
Vc	distribution volume
video-EEG	video-electroencephalogram

10.11 Appendix 11: Protocol amendment history

Amendment 1 (13 Oct 2020)

Overall Rationale for the Amendment

Changes to the protocol have been made to simplify the study logistics, to update secondary objectives, to provide updated data from the pediatric PK model, and to improve consistency within the protocol. Minor grammatical, editorial, and formatting changes have also been made for clarification purposes only.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of activities 3 Objectives and endpoints 9.3.2 Analysis of the secondary efficacy endpoints 9.3.2.1 Time to response 9.3.2.2 Time to seizure freedom	Reduce the video-EEG time from 96 hours to 48 hours.	Reducing the video-EEG time helps to preserve the skin of the neonates, and allows the video-EEG machines to be available for other patients in the NICU.
1.1 Synopsis 4.1.2 Study periods 6.3 Measures to minimize bias: Randomization 11 References	Remove the response-adaptive design such that all study participants are enrolled in a 1:1 randomization schedule.	Response-adaptive design works optimally with planned enrollment whereby treatment response is fully incorporated into a new randomization vector before the next randomization occurs. Given the uncertainty of the enrollment rate, and the interval between participants enrolling in this study, the randomization ratio was set at 1:1 to ensure accurate study enrollment status is provided at the time of informed consent for each potential participant.
1.1 Synopsis 3 Objectives and Endpoints 9.3.2 Analysis of the secondary efficacy endpoints	Secondary endpoints were updated with 4 new endpoints: • Absolute reduction in seizure burden across the first 48-hours of the Treatment Period measured by continuous video-EEG compared with the Baseline video-EEG • Percent reduction in seizure burden across the first 48-hours of the Treatment Period measured by	To provide a different evaluation of efficacy, based on a reduction of seizure burden, rather than proportion of responders.

	continuous video-EEG compared with the Baseline video-EEG • Proportion of responders at the end of the first 48-hours of the Treatment Period • Proportion of study participants who are seizure-free (100% reduction in seizure burden from Baseline) at 24 hours after the start of the Treatment Period, categorized by study participants with nonsevere or severe seizure burden at Baseline	
9.9 Determination of sample size	The following text was added: **In addition, the sample size was estimated based on seizure count data rather than seizure burden (min/hour) due to the unavailability of the seizure burden data for neonates.**	To provide greater transparency in the description of the sample size calculation.
1.1 Synopsis 4.1.2 Study periods 6.3 Measures to minimize bias: Randomization	Sections updated to note that randomization will be stratified by seizure severity.	To add clarity to the protocol.
9.3.2.1 Time to response 9.3.2.2 Time to seizure freedom	The following sentence has been added to these sections. **The 95% CI will be provided for descriptive purposes only.**	To provide additional detail to the efficacy analyses.
8.6.1 Pharmacokinetic sampling and handling	Removal of the option to assess the PK of LCM using the commercial assay processed in the sites laboratory. The description of the analysis of the PK samples moved to the end of the section.	The use of a central laboratory for all PK samples removes the need for cross-validation between laboratories, and the shipment of an extra sample.
1.1 Synopsis 3 Objectives and endpoints 4.1.2 Study periods 4.3 Justification for dose 8.5 Treatment of overdose	Text updated to confirm that concentrations of LCM will be calculated only from serum (and not plasma/serum).	For accuracy in the Protocol.

9.1 Definition of analysis sets 9.5 Handling of protocol deviations		
4.1.2 Study periods 8.6.1 Pharmacokinetic sampling and handling	The total volume of the PK sample has been edited from 200µL/sample to 0.2mL/sample.	To ensure consistency in the units of measurement of the PK sample throughout the protocol.
2.3 Benefit/Risk Assessment 4.3 Justification for dose	Text updated throughout the section to reflect the most current data from the pediatric population PK model.	The pediatric population PK model was updated.
1.1 Synopsis 4.1.2 Study periods	Text updated with a revised LCM dose of 15mg/kg/day: A dose of LCM ~~18~~**15**mg/kg/day is estimated to yield approximately the same plasma concentrations as in an adult receiving LCM 400mg/day.	As a result of an update to the pediatric population PK model, the dose has been updated.
Table 1-1 Schedule of Activities – Screening and Treatment Periods	Updated the row "LCM PK samples" and updated Footnote p to indicate that PK sampling times are detailed in Table 1-3.	For accuracy and consistency within the protocol.
Table 1.3 Schedule for PK sampling	Footnote b removed. Footnote a updated with preferably and removal of either: One optional sample per day, **preferably** obtained ~~either~~ shortly before dosing (trough sample) or at any other postdose time point (but never during infusion)	To remove conflicting information and improve clarity.
8.6.3 Pharmacokinetic analysis 9.5 Planned pharmacokinetic analyses	Content updated to remove the estimation of relevant individual PK parameters.	The number of samples collected for PK sampling is sparse. With only a few samples per study participant, the estimation of individual PK values cannot be performed reliably.
8.6.3 Pharmacokinetic analysis	Content updated to confirm that data from SP0968 will be used to update the LCM population PK model at the end of the study.	To distinguish the update of the population PK model from the interim review of LCM dose and serum concentrations during the study which is conducted to ascertain if a dose change during the study is required.
1.1 Synopsis Figure 1-1 Schematic overview of the study	Content amended to clarify that all study participants will enter the SFU period, that the SFU	The day of the SFU visit had been previously omitted. Added for accuracy and clarity.

Table 1-2 Schedule of Activities – Extension and Safety Follow-up Periods 4.1.2 Study periods	visit will occur at the end of the SFU period (Day 14 ± 2 days), and that down-titration of LCM dose may take place over 7 days.	
5.2 Exclusion criteria	Criterion #9 amended. The assessment of kidney function is to be calculated using the revised Schwartz formula.	Creatinine clearance is not checked directly in neonatal infants. The Schwartz formula is considered the best method for estimating glomerular filtration rate in children.
1.3 Schedule of activities 8.2.4 HIE (Thompson score) 9.4 Planned safety analyses 11 References	Removal of the Thompson score from the safety assessments.	The Thompson score is not routinely used in NICUs. The Sarnat assessment which also assesses the severity of HIE will remain.
7.1.1 Liver stopping criteria – potential drug-induced liver injury	The PDILI criterion #2 has been amended, and the following sentence removed: In case AST, ALT, or ALP elevation ≥5x ULN occurs within 5 days after birth, study drug must be discontinued and LFTs retested within 24 hours. ~~If AST, ALT, and ALP are confirmed to be <5x ULN, the study participant may restart study drug after consultation with and approval by the Medical Monitor~~.	Restarting study drug is not possible after the end of an acute phase of seizures.
8.2.1 Medical history including Apgar score	The following sentence has been amended to include 5. The score is reported at 1**, 5** and 10 minutes after birth	Correction of text.

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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

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