STATISTICAL ANALYSIS PLAN

Study: SP0968

Product: Lacosamide

A MULTICENTER, OPEN-LABEL, RANDOMIZED, ACTIVE COMPARATOR STUDY TO EVALUATE EFFICACY, SAFETY, AND PHARMACOKINETICS OF LACOSAMIDE IN NEONATES WITH REPEATED ELECTROENCEPHALOGRAPHIC NEONATAL SEIZURES – PHASE 2/3

SAP/Amendment Number	Date
Final SAP	24 Sep 2020
SAP Amendment 1	05 Mar 2021
SAP Amendment 2	14 Apr 2022
SAP Amendment 3	04 May 2023

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BZD	benzodiazepine
CGA	corrected gestational age
CI	confidence interval
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CV	coefficient of variation
d	day
DBP	diastolic blood pressure
DEM	data evaluation meeting
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
ENS	electroencephalographic neonatal seizures
FAS	Full Analysis Set
FDA	Food and Drug Administration
GA	gestational age
geoCV	geometric coefficient of variation
geoMean	geometric mean
h	hour/-s
HIE	hypoxic-ischemic encephalopathy
ICF	informed consent form
INR	international normalized ratio
IPD	important protocol deviations
LCM	lacosamide
LDC	lidocaine
LEV	levetiracetam
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
min/h	minutes per hour
NICU	Neonatal Intensive Care Unit
nR	normalized ratio
PB	phenobarbital
PDILI	potential drug-induced liver injury
PHT	phenytoin
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set

PMA	postmenstrual age
PNA	postnatal age
PPS	Per-Protocol Set
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SFU	safety follow-up
SOC	system organ class
SS	Safety Set
StOC	standard of care
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of the statistical methodology to be used for the analyses of data collected to support the final clinical study report for SP0968 (Phase 2/3). The SAP is based on Protocol Amendment 2, dated 11 February 2022.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to evaluate the efficacy of Lacosamide (LCM) vs an Active Comparator chosen based on standard of care (StOC) in severe and non-severe seizure burden (defined as total minutes of electroencephalographic neonatal seizures [ENS] per hour) in neonates with seizures that are not adequately controlled with previous anti-epileptic drug (AED) treatment.

2.1.2 Secondary objectives

The secondary objectives are:

- To further evaluate the efficacy of LCM vs an Active Comparator in severe and non-severe seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that are not adequately controlled with previous AED treatment
- To evaluate the short-term safety and tolerability of LCM in neonates
- To evaluate the pharmacokinetics (PK) of LCM in neonates who have seizures that are not adequately controlled with previous AED treatment

2.1.3 Other objectives

- To further evaluate the short-term safety and tolerability of LCM in neonates

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable is as follows:

- Reduction in seizure burden measured in the Evaluation video-electroencephalogram (video-EEG) compared with the Baseline video-EEG. The 2-hour evaluation for efficacy will start 1 hour after initiation of randomized treatment (LCM or Active Comparator).

2.2.1.2 Secondary efficacy variables

- Proportion of responders in the Evaluation video-EEG compared with the Baseline video-EEG
- Proportion of participants with at least 80% reduction in seizure burden in the Evaluation 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 non-severe or severe seizure burden at Baseline
- Categorized percentage reduction in seizure burden in the Evaluation video-EEG compared with the Baseline video-EEG (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)

2.2.2 Safety variables

2.2.2.1 Secondary safety variable

The secondary safety variables are as follows:

- Treatment-emergent adverse events (TEAEs) as reported by the Investigator
- Percentage of treatment-emergent marked abnormalities in 12-lead electrocardiogram (ECG)

2.2.2.2 Other safety variables

- Percentage of treatment-emergent marked abnormalities in hematology and chemistry parameters
- Percentage of treatment-emergent marked abnormalities in vital sign measurements (i.e. blood pressure 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.

2.2.3 Pharmacokinetic variables

- Serum concentration of LCM (µg/mL)

2.3 Study design and conduct

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.

Study 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 (phenobarbital [PB], levetiracetam [LEV], or midazolam [MDZ] in any combination; additional benzodiazepines are allowed) will be enrolled in the study.

Per Protocol Amendment 1, participants must be at least 34 weeks of gestational age (GA) at enrollment. In addition, term neonates up to 28 days of postnatal age (PNA) and preterm neonates up to 40 weeks of postmenstrual age (PMA) and 28 days of PNA can be enrolled, at the time of signing the informed consent.

Per Protocol Amendment 2, participants must be ≥34 weeks of corrected gestational age (CGA), <46 weeks of CGA, and <28 days of PNA at the time of signing the informed consent.

The study involves a Screening Period of up to 36 hours followed by a 96-hour Treatment Period during which study participants will 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 (or at least 1 hour before treatment randomization for participants enrolled under Protocol Amendment 1) 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 complete the study or who discontinue randomized treatment during either 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 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 at Baseline (non-severe or severe, as determined by the Investigator).

2.3.1 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 (or at least 1 hour before treatment randomization for participants enrolled under Protocol Amendment 1) and will continue for 48 hours after administration of the first dose of randomized treatment. The Baseline 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 an independent central reader. The independent central reader will be blinded from the study participant's medical history and randomized treatment. The video-EEG data should be saved, stored, anonymized, and delivered to the independent central reader in an expeditious manner.

2.4 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 phenytoin (PHT). Two major studies in first-line treatment of neonatal seizures have shown enormous differences in responder rates to PB vs LEV (80% vs 28%; 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 benzodiazepine (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 2–1.

Table 2–1: 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 = 20%)
1	-0.82	35%
2	-0.7	30%
3	-0.6	24%

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, participant data listings, and statistical output will be performed using SAS Version 9.4 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of participants in each category will be presented. Unless otherwise noted, all percentages and derived variables will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. The denominator for all percentages will be the number of participants in the treatment group within the analysis set of interest, unless otherwise noted.

For continuous parameters, descriptive statistics will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer
- Mean, SD, and median will use 1 additional decimal place compared to the original data
- Minimum and maximum will have the same number of decimal places as the original data

The individual PK concentrations will be reported to 3 significant figures in the listing. The descriptive statistics will be rounded to 4 significant figures for the mean, geoMean, median, SD, and confidence interval (CI), to 1 decimal place for geoCV and to 3 significant figures for the min, max. Values >1000 will be rounded to the nearest integer.

In general, the maximum number of decimal places reported should be 4 for any summary statistics.

The 90% credible intervals and the 95% CIs will be presented to 1 decimal place, and the posterior probability will be presented to 2 decimal places.

A complete set of listings containing all documented data and all calculated data (e.g., change from Baseline) will be generated, and will be sorted by site, participant number and time point (where applicable).

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day and time

For measurements with date and time collected, relative day and time will be calculated.

Relative day and time in 24-h clock will be calculated as current date minus first dose date, current time in hours minus first dose time in hours, current time in minutes minus first dose time in minutes (adding 1 minute if the current date and time is the same or after the first dose date and time, for measurements obtained during treatment). This will then be converted to a time in hours, where 1 day has 24 hours and 1 minute is 1/60 of an hour.

If the current date and time is the same as the first dose date and time, the relative minute is "1" or "0.0166 h". If the current date and time is prior to the first dose date and time, then the relative day and time will be denoted by "-". If the date and time is after the date and time of last study medication administration (as defined in Section 4.2.4) then the relative day and time will be calculated relative to the date and time of last study medication administration and prefixed with a "+". The relative day and time in listings will be displayed in hours.

- Example 1: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 5-Jan-2017: 8:45 am. The relative day and time are calculated as 5-Jan-2017 minus 5-Jan-2017=0, 8:00 h – 10:00 h= -2:00 h, 45 min-30 min=15 min. The relative day and time is -0 d 1 h 45 min, i.e. -1 h 45 min or -1.75 h
- Example 2: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 7-Jan-2017: 8:45 am. The relative day and time is calculated as 7-Jan-2017 minus 5-Jan-2017=2 d (48 h), 8:00 h – 10:00 h= -2:00 h, 45 min-30 min + 1 min=16 min. The relative day and time is 1 d 22 h 16 min or 46.2667 h
- Example 3: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 3-Jan-2017: 8:45 am. The relative day and time is calculated as 3-Jan-2017 minus 5-Jan-2017= -2 d (-48 h), 8:00 h – 10:00 h= -2:00 h, 45 min-30 min=15 min. The relative day and time is -2 d 1 h 45 min or -49.75 h

Relative day and time will be displayed with up to 4 decimal places. Relative day and time will not be calculated for partial dates and times.

3.2.1.2 Relative day

For measurements with only date collected, relative day will be calculated. Relative day will be calculated as the date of first dose of study medication minus the current date for days prior to the first dose of study medication. During treatment (from the day of first study medication dose until the day of last study medication dose), relative day will be calculated as the current date minus the date of first dose of study medication plus 1 (eg, the day of first dose will be Day 1 and the day prior to first dose will be Day -1). For days after the last dose of study medication, relative day will be calculated as the current date minus the date of last study medication dose and will include a '+' to denote post-treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

3.2.2 Study periods for analysis

3.2.2.1 Screening Period (-36 hour to 0 hour)

The Screening Period will start from the signing and dating of the written informed consent form (ICF) and is up to 36 hours prior to the initiation of the first dose of randomized study treatment. During this period, study participants must have been administered StOC treatment (based on local practice and treatment guidelines). The previous AED treatments may have been administered at a location other than the study site.

3.2.2.1.1 Baseline Period (-2 hour to 0 hour)

Baseline is defined as the final 2 hours of the Screening Period (or the final 1 hour of the Screening Period for participants enrolled under Protocol Amendment 1). During this period, study participants will continue to receive the standard of care of the Neonatal Intensive Care Unit (NICU) and the AED treatment must not be changed. Baseline assessments, including assessment of seizure burden, need to be conducted before randomization. The interpretation of the Baseline video-EEG by the Investigator should be done immediately before randomization.

3.2.2.2 Treatment Period (0 hour to 96 hour)

The Treatment Period will continue through 96 hours or until the decision to stop treatment is made.

3.2.2.2.1 Evaluation Period (end of first hour to the third hour)

The 2-hour Evaluation Period 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.

3.2.2.3 Extension Period (up to 28 days of postnatal age)

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.

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

Study participants who complete their Extension Period or discontinue randomized treatment (either from Treatment or Extension Period), will enter the SFU Period.

For study participants in the LCM treatment group, the SFU Period includes an option to down titrate their LCM dose. Down titration (for 7 days) 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.

3.2.2.5 Analysis phases

For the purposes of analysis, data (including adverse events [AEs] and concomitant medical procedures) will be assigned to 1 of the following phases:

- Pre-treatment
  - All events and procedures with onset prior to the first dose of randomized study medication.
- On-treatment
  - All events and procedures with onset on or after the first dose of randomized study medication and on or before the last dose of study medication.
- Post-treatment
  - All events and procedures with onset after the last dose of randomized study medication.

If down titration occurs prior to discharge and is recorded in the electronic Case Report Form (eCRF) then the on-treatment phase will include the down titration period. Exposure will be calculated for the on-treatment phase as described in Section 10.1.

3.2.3 Mapping of assessments performed at Early Withdrawal and in the Extension Period

Safety assessments at Early Withdrawal that correspond to a scheduled time point will be included in the summaries for that time point if the assessment was scheduled to occur and if there is not already an assessment recorded for that time point. In particular, vital signs, body weight, ECG, laboratory parameters and PK samples are collected at different time points of the Treatment Period. All assessments of these variables at Early Withdrawal corresponding to a scheduled time point will be mapped to the corresponding scheduled time point if they fall within the following windows:

- within 15 minutes of the 3-hour time point

- within 3 hours of the 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88 and 96-hour time points (with the exception of laboratory assessments)
- within 12 hours of the 24 and 96-hour time points for laboratory assessments

For participants enrolled under Protocol Amendment 2 and randomized to LCM there is a scheduled 12-lead ECG assessment at 1 to 6 hours after the first dose of LCM. Any 12-lead ECG assessment performed at Early Withdrawal for such participants will be mapped to this scheduled time point if it occurs within the same window (ie, 1 to 6 hours) after the first dose (and the assessment at this time point was not otherwise performed).

Safety assessments in the Extension Period (including Early Withdrawal assessments) will be mapped to a scheduled visit if they occur within 2 days of the scheduled day for that visit, e.g. on or between relative days 9 and 13 for the Week 1 visit, relative days 16 and 20 for the Week 2 visit, and relative days 23 and 27 for the Week 3 visit (based on visits occurring every 7 days in the Extension Period, with a permitted tolerance window of ±2 days).

If there are multiple Early Withdrawal assessments corresponding to a scheduled time point or visit, the earliest non-missing assessment will be mapped to the scheduled time point or visit and used for summary statistics or frequency counts. Similarly, if there are multiple assessments performed and recorded at the same scheduled time point or visit, the earliest non-missing assessment will be used for summary statistics or frequency counts.

No mapping of unscheduled visits will be performed with the exception of unscheduled visits used as Baseline. If an unscheduled measurement is selected as the Baseline (as described in Section 3.3), this value will be included in the summary statistics for the Baseline time point in all tabulations.

Early Withdrawal and Extension Period assessments which have been mapped to a scheduled time point or visit will be included in summary tables at the scheduled time point/visit. Unscheduled assessments as well as Early Withdrawal and Extension Period assessments which are not mapped to a scheduled time point or visit will be included in listings only.

3.2.4 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.

3.2.5 Definition of completed study

For disposition summaries, participant completion status will be determined from the Study Termination eCRF.

3.3 Definition of Baseline values

In general, Baseline value for safety will be defined as the latest value prior to the first dose of study drug (LCM or Active Comparator), unless otherwise noted for a specific type of data. Both scheduled and unscheduled assessments are considered. Assessments performed after the start time of the first randomized dose of study medication will not be considered for Baseline.

Baseline for efficacy is defined in the efficacy analysis section (Section 8).

3.4 Analysis sets

3.4.1 All Participants Screened Set

The All Participants Screened Set will consist of all study participants with a signed completed ICF as reported on the eCRF.

3.4.2 Safety Set

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.

3.4.3 Full Analysis Set

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 Baseline and the period between 1 and 3 hours (Evaluation Period) after randomization to the initial study medication treatment. The primary analysis set for the efficacy data will be the FAS.

Participants with severe seizure burden (as determined by the Investigator) may also be included in the FAS if they have 15 to 30 minutes of interpretable video-EEG at Baseline.

Participants with no qualifying seizures on the Baseline video-EEG (up to 2 hours prior to the first dose of randomized study medication) will be excluded from the FAS.

3.4.4 Per-Protocol Set

Per-Protocol Set (PPS) will include all participants in the FAS who did not have important protocol deviations (IPD) related to efficacy. The secondary analysis set for the efficacy data will be the PPS.

3.4.5 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) 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. Participants with IPDs related to PK may be excluded following discussion at IPD meetings.

3.5 Treatment assignment and treatment groups

Treatment groups will be assigned based on 1:1 randomization to either LCM or Active Comparator. Randomization will be stratified by seizure severity (severe seizure burden versus non-severe seizure burden, as determined by the Investigator).

Participants will be summarized according to the actual/received treatment for the All Participants Screened Set, SS, and PK-PPS, and according to the planned (randomized) treatment group for the FAS and PPS.

3.6 Center pooling strategy

There is no differentiation by center in this study, ie, the data will be analyzed from all centers together.

3.7 Coding dictionaries

Medical history (if available) and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version September 2013. Medical procedures will not be coded.

3.8 Changes to the protocol-defined analysis

The following changes to the protocol were made:

- The protocol states that the video-EEG central reader will be blinded to study site and participant medical history. This was updated as the central reader will be blinded to participants' medical history and randomized treatment but not to the study site.
- The protocol states that participants with 30 minutes of interpretable video-EEG at Baseline and in the first 3 hours after randomization to the initial study medication treatment will be included in the FAS. This was updated to participants with 30 minutes of interpretable video-EEG at Baseline and in the period between 1 and 3 hours after randomization, as the primary analysis is on the 1 to 3 hour period (Evaluation Period). The definition of the FAS was also expanded to include participants with severe seizure burden (as determined by the Investigator) with only 15-30 minutes of interpretable video-EEG at Baseline. This is to allow for participants with status epilepticus who can be included with a minimum of 15 minutes of video-EEG as per the protocol. Any participants who do not have qualifying seizures on the Baseline video-EEG will be excluded from the FAS as such participants will not be included in the efficacy analyses.
- The protocol states that the PK-PPS 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. This was updated to add that participants with IPDs related to PK may be excluded following discussion at IPD meetings.
- The protocol states that efficacy and safety summaries will be repeated for the following subgroups for primary cause of seizure: hypoxic-ischemic encephalopathy (HIE), hemorrhage, or infarction; central nervous system (CNS) malformations; CNS infections;

undetermined causes. The 'undetermined causes' group was changed to 'Other', to also include participants with epileptic encephalopathy/genetic epilepsy, inborn error of metabolism or 'other' as their primary cause of seizure as reported on the eCRF. In addition, the safety summaries by primary cause of seizure were not reported as these were not considered to be clinically meaningful on a small number of participants.

- The protocol states that physical examination will be reported at 24 hours, 48 hours, 72 hours and 96 hours. These will no longer be reported separately. Clinically significant abnormalities identified during the physical examination will be recorded as AEs and included in the AE summaries.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The primary efficacy analysis and planned sensitivity analyses will be adjusted for log-transformed Baseline seizure burden (based on data provided by the central reader) and seizure severity (as determined by the Investigator at Baseline) in the analysis of covariance (ANCOVA) models in the Bayesian framework.
If the study is stopped for any reason prior to the completion of enrollment (ie, fewer than 32 participants randomized and dosed), no adjustments for covariates will be performed.

4.2 Handling of dropouts or missing data

There will be no specific imputation of missing data except for missing dates and/or times for concomitant medication and AEs.

The handling of missing dates and times for seizures, if applicable, will be discussed during the Data Evaluation Meeting (DEM).

4.2.1 Handling of prior and concomitant medications with missing data

Any medications with incomplete start and end dates and/or times (excluding those collected on the Mother's Medication Regimen at the Time of Delivery eCRF page and those collected on the Active Comparator Treatment eCRF page) will be handled according to the following rules for classification as prior and concomitant and for determining if these were taken during the Treatment Period (as required for the efficacy analysis). Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

Imputation of partial start dates:

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start date, then use the date of first dose. If this results in start date after a known or partial end date, use the 1st of the month.
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use January 1st of the year of the start date.

- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose. If this results in start date after a known or partial end date, use January 1st of the year of the start date.
- If the date is completely unknown, then use the date of first dose. If this results in start date after a known or partial end date, use the participant's date of birth.

Imputation of partial or missing start times (for rescue medications only):

- If the start time of the medication is missing and the start date (or imputed start date) is the same as the date of the first dose, then use the time of the first dose.
- If the start time of the medication is missing and the start date (or imputed start date) is not the same as the date of the first dose, then impute the time as 00:00h.
- If the start time of the medication is partial the following rules will apply:
  - If the minutes are missing, impute as either HH:00 (using the known hour) or with the time of the first dose if the known hour is the same as the hour of the first dose and the date is the same.
  - If the hour is missing, impute as either 00:MM (using the known minutes) or with the time of the first dose if the known date is the same as the first date of dosing.

In all rules specified above, the date of first dose refers to the first dose administered during the Treatment Period.

Imputation of partial end dates:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31st of that year.
- If the participant dies and an imputed partial end date falls after the date of death, the date of death should be used.
- If the date is completely unknown, do not impute the stop date.

Partial or missing end times will not be imputed.

There will be no imputation of any other missing concomitant medication data. In addition, all the imputed dates will be carried over after ensuring that no imputed date will be prior to the date of birth of the neonate. The date of birth of the neonate will be considered as the start date if no more other information is provided.

In case of uncoded medications, these medications should be designated as "Coding-pending", and such medications will be included in summary tables and participant listings based on this classification.

4.2.2 Handling of adverse events with missing data

Any AEs with incomplete onset and outcome (end) dates/times will be handled according to the following rules for classification as treatment-emergent. Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

- If the date is specified but the time is missing and the date is the same as the date of first study medication administration, then use the time of first study medication administration. If this results in a start date and time after a known or partial end date and time, then use 00:00h.
- If the date is specified and the time is missing and the date is not the same as the date of first study medication administration, then use 00:00h.
- If only the month and year are specified and the month and year of first dose is not the same as the month and year of onset, then use 00:00h on the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of onset, then use the date/time of first dose. If this results in a start date after a known or partial end date, then use 00:00h on the 1st of the month.
- If only the year is specified, and the year of first dose is not the same as the year of onset, then use 00:00h on January 1st of the year of onset.
- If only the year is specified, and the year of first dose is the same as the year of onset, then use the date/time of first dose. If this results in a start date after a known or partial end date, then use 00:00h on January 1st of the year of onset.
- If the AE onset date is completely unknown, then use the date and time of first dose. If this results in a start date and time after a known or partial end date and time, then use 00:00h on January 1st of the year of the end date.
- Imputations for missing end dates/times will not be performed for classification as treatment-emergent as this is not required.

In all rules specified above, the date of first dose refers to the first dose administered during the Treatment Period. In addition, all the imputed dates will be carried over after ensuring that no imputed date or time will be prior to the date and time of birth of the neonate. The date and time of the birth of the neonate will be considered as the start date and time if no more other information is provided (00:00h will be used if the time of birth is missing).

Adverse events with missing severity or causality will be regarded as 'severe' and 'related' respectively for the tabulations. There will be no imputation of any other missing AE data. Any AE with additional missing data that prohibits classification for a given tabulation will be excluded from that tabulation.

In case of uncoded AEs, these AEs should be designated as "Coding-pending", and such AEs will be included in summary tables and participant listings based on this classification.

4.2.3 Handling of dropouts or missing efficacy data

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

4.2.4 Handling of study medication with missing data

No imputation should be performed for missing study medication start dates. This field on the eCRF should not be partial or missing.

For partial or missing date of last dose of study medication on the Study Termination eCRF the following imputation rules will be applied for the purpose of calculating overall exposure:

- If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the Study Termination eCRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the Study Termination eCRF.
- If a participant died and has a partial or missing last administration date, the date is to set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.
- If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact per the Study Termination eCRF. A review of the data for participants with completely missing last dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.
- Time of last dose is not recorded on the Study Termination eCRF.
  - For participants randomized to LCM, the time of the last dose (or end time for infusions) will be obtained from the latest time reported on the individual LCM dose administration eCRF (LCM Infusion or LCM Oral eCRF) for all doses reported on the corresponding date (if available).
  - For participants randomized to Active Comparator, if the end date on the Active Comparator Treatment eCRF matches the date of last study medication on the Study Termination eCRF then the time of the last dose will be obtained from the end time on the Active Comparator Treatment eCRF.
  - If the time cannot be determined, then the time will be imputed as 23:59.

Imputed date of last dose should only be used for calculation of the duration of exposure, relative day/time, and determining concomitant medications. The date as recorded on the eCRF should be presented in participant data listings (no imputed dates should be included in participant data listings).

4.2.5 Potential impact of Coronavirus Disease 2019 on dropouts or missing data

The Coronavirus Disease 2019 (COVID-19) pandemic may cause disruption in the conduct of ongoing clinical trials including treatment and study withdrawals, participants missing study visits, and/or visits being performed remotely instead of at site. Sites will complete the COVID-19 Impact eCRF page in case a participant was impacted by COVID-19 during the study. The COVID-19 Impact eCRF page will include the timing and impact of COVID-19, and relationship to COVID-19 (ie, whether the participant has confirmed/suspected COVID-19 infection, or whether the impact was related to general circumstances around COVID-19 without infection).

4.3 Interim analyses 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 Patient Safety 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. Listings of seizure burden will also be presented. The objective, procedures, and timing of DMC safety assessments to evaluate risk and benefit for study participants in SP0968 are described in the DMC Charter.

4.4 Multicenter studies

The results will not be presented by individual center.

4.5 Multiple comparisons/multiplicity

There will be no adjustment for multiplicity in this study.

4.6 Use of an efficacy subset of participants

The efficacy analysis will be based on the FAS.

4.7 Active-control studies intended to show equivalence

This section is not applicable for this study.

4.8 Examination of subgroups

The primary efficacy endpoint will be analyzed by the following subgroups as a sensitivity analysis:

1. Primary cause of seizure subgroups (based on most recent assessment available):
   - HIE, hemorrhage or infarction (including HIE, ischemic stroke and intracranial hemorrhage)
   - CNS malformations (brain malformation)
   - CNS infections (intracranial infection)
   - Other (including epileptic encephalopathy/genetic epilepsy, inborn error of metabolism, undetermined cause and other)
2. Concomitant use of hypothermia subgroups: yes, no
   - The concomitant hypothermia treatment subgroup is defined as ‘Yes’ for all participants with any documented concomitant hypothermia treatment as per the dedicated eCRF page.

5 STUDY POPULATION CHARACTERISTICS

5.1 Participant disposition

The number of screen failures and the primary reason for screen failure will be summarized for all participants screened (ie, all study participants with a signed ICF).

Disposition of study participants screened will be summarized by treatment group (LCM and Active Comparator): the date of first participant in, date of last participant out (latest scheduled or unscheduled visit), and the number of enrolled study participants will be summarized for all study sites and by study site. Additionally, the number of study participants in each of the SS, FAS, PPS, and PK-PPS will be summarized.

Disposition and discontinuation reasons by period will be summarized for the following:

- Study participants randomized
- Study participants entering the Treatment Period (defined as receiving at least one dose)
- Study participants completing the Evaluation Period (defined as completing 3 hours of video-EEG monitoring after the first administration of study medication, regardless of interruptions)
- Study participants completing 30 minutes of video-EEG in the Evaluation Period (defined as at least 30 minutes of interpretable video-EEG data available between 1 and 3 hours after the first administration of study medication).
- Study participants completing 48 hours of video-EEG monitoring after the first administration of study medication.
  - Participants are considered as completing 48 hours of video-EEG if data are available for the analysis of the 48 hour time point, ie, a minimum of 30 minutes of video-EEG are available between 44 and 48 hours after the first dose, as described in Section 8.2.3.
- Study participants with a SFU visit
- Study participants completing the study (based on the Study Termination eCRF)
- Study participants discontinuing the study and primary reason for discontinuation (based on the Study Termination eCRF)

All percentages will be relative to the number of study participants in the SS.

In addition, discontinuation due to AEs will be summarized separately for the SS. Listings of rescreened participants, study participants who did not meet study eligibility criteria, participant disposition (including Active Comparator treatments for participants who received Active Comparator treatment), and participant analysis sets will be provided for all study participants screened. A listing of participant discontinuation, based on the SS, will be presented and will include the total days on study medication, calculated as the date of last dose (from the Study Termination eCRF) minus the date of first dose +1. A listing of the planned (randomized) and actual treatments for all participants in the SS will also be provided.

A summary of the number of participants receiving each of the Active Comparator treatments (PB, PHT, LEV, lidocaine [LDC], MDZ, lignocaine, fosphenytoin and other) will be provided, based on the SS.

5.2 Protocol deviations

The number and percentage of study participants with no IPDs and at least 1 IPD will be summarized overall, and by main category of protocol deviation (inclusion criteria deviation, exclusion criteria deviation, withdrawal criteria deviation, prohibited concomitant medication use, incorrect treatment or dose, treatment non-compliance, procedural non-compliance), based on the FAS. Additionally, the number and percentage of study participants excluded from the PPS due to IPDs will be summarized overall and by main protocol deviation category for the FAS. Other specific categories of protocol deviations will be defined within the IPD specifications document.

A listing of study participants excluded from the efficacy analysis will be provided, based on the SS.

A listing of IPDs will be provided for the SS.

All completed COVID-19 Impact eCRF pages and other IPDs will be reviewed during IPD meetings in order to determine if any such events are to be considered and reported as IPDs.

All data collected from the COVID-19 Impact eCRF page will be listed based on the All Participants Screened Set.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and baseline characteristics

Demographic variables will be presented by treatment group for the SS and the FAS. The variables to be considered are:

- Gestational age (weeks), calculated as the gestational age in days divided by 7.
  - Gestational age in weeks will be presented (rounded) to 1 decimal place in the data listings.
- Postnatal age (days)
- Gestational age category (Pre-term <37 weeks vs Full term ≥37 weeks)
  - Gestational age category will be based on complete weeks only without rounding ie, a gestational age of 36.7 weeks will not be rounded to 37 weeks.
- Gender
- Weight (kg)
- Length (cm)
- Head circumference (cm)
- Racial group (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other or Mixed)
- Ethnicity (Hispanic or Latino/Not Hispanic or Latino)
- Country (Australia, Canada, and United States)

The following Baseline characteristics will be presented by treatment group for the FAS, PPS, and SS:

- Apgar score (1 minute after birth)
- Apgar score (5 minutes after birth)
- Apgar score (10 minutes after birth)
- Baseline seizure burden severity (non-severe, severe), as determined by the Investigator

- Primary cause of seizure (HIE, hemorrhage or infarction; CNS malformations; CNS infections; Other), based on most recent assessment available
- Concomitant hypothermia treatment (yes/no)

The listings of demographics and Baseline characteristics will be provided for all study participants in the SS.

6.2 Medical history and concomitant diseases

The number and percentage of study participants with a medical history (if available) condition including both resolved and ongoing conditions at the time of screening will be summarized overall and by MedDRA primary system organ class (SOC) and preferred term (PT) for the SS.

Listings of medical history glossary and medical history (if available) will be provided for the SS.

6.3 Prior, concomitant, and follow-up medications

Each medication recorded on the Prior and Concomitant Medications eCRF will be classified as either an AED or a non-AED medication based on the coded WHO-DD preferred drug name. The classification of such medications will be confirmed by the Study Physician prior to database lock. A listing of prior, concomitant, and follow-up medications, indicating whether the medication is classified as an AED, will be provided for the SS. A glossary of all prior, concomitant, and follow-up medications, indicating AED and non-AED medications, will be provided for the SS.

6.3.1 Prior medications

Medications with the start date and time prior to the first dose of randomized study medication are considered prior medications, including medications which are ongoing after the first dose.

6.3.2 Concomitant medications

Medications that were taken on at least one day in common with the study medication dosing period (including dosing in the Treatment Period, Extension Period and SFU Periods) are defined as concomitant medications. This definition includes 1) medications with the start date and time on or after the date and time of the first dose of study medication up to and including the last dose of study medication (as defined in Section 4.2.4), 2) medications with the start date and time prior to the date and time of the first dose of study medication but with the stop date and time on or after the date and time of first dose of study medication. Where possible, concomitant medications are classified by date and time. If the time is not available, then the classification will be based on the date only.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant. A medication may be considered as both prior and concomitant.

6.3.3 Follow-up medications

Medications that were taken after the date and time of last dose of study medication (as defined in Section 4.2.4) are defined as follow-up medications. This definition includes 1) medications with the start date and time prior to the last dose of study medication and continuing after the last

dose of study medication and 2) medications with the start date and time after the date and time of the last dose of study medication.

A medication starting prior to the first dose of randomized study medication and continuing throughout the study into the SFU Period will be classified as prior, concomitant and follow-up.

6.3.4 Rescue medications

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 excluded from the primary efficacy analysis and treated as non-responders for secondary responder endpoints.

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

Rescue medications will be identified by the Investigator on the Prior and Concomitant Medications eCRF. The number and percentage of study participants who received rescue medication will be summarized by WHO-DD preferred drug name for the SS.

6.3.5 Prior non-AED medications

The number and percentage of study participants taking prior non-AED medications will be presented by treatment group and overall for the SS and summarized by WHO-DD pharmacological group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2) and preferred drug name for the SS.

6.3.6 Prior AEDs

The number and percentage of study participants taking prior AED medications will be presented overall by treatment group and overall for the SS and summarized by WHO-DD preferred drug name for the SS.

6.3.7 Concomitant non-AEDs

The number and percentage of study participants taking concomitant non-AED medications will be presented by treatment group and overall for the SS and summarized by WHO-DD pharmacological group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2) and preferred drug name for the SS.

6.3.8 Concomitant AEDs

The number and percentage of study participants taking concomitant AEDs will be summarized by WHO-DD preferred drug name for the SS. Participant data listing for concomitant AEDs will be provided for the SS and will include a column identifying rescue medications.

6.4 Procedure history

Listing of procedure history will be provided for the SS.

6.5 Concomitant medical procedures

Listing of concomitant medical procedures will be provided for the SS.

6.6 Primary cause of seizure

Primary cause of seizure will be summarized by treatment group and overall for the SS. The summary analysis of the primary cause of seizure will be based on the latest data collected per participant prior to study completion/termination and will summarize the causes as recorded on the eCRF (HIE, ischemic stroke, intracranial hemorrhage, epileptic encephalopathy/genetic epilepsy, intracranial infection, brain malformation, inborn error of metabolism, undetermined cause, other). Listing of all primary causes of seizure will be provided for the SS and will include the primary cause of seizure as reported on the eCRF and the categorization as defined in Section 4.8.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

7.1 Treatment compliance and drug accountability

For LCM infusions, the start date and time, end date and time, kit number, location of infusion, dose, volume, and notable events will be recorded for each administration. For oral LCM, the date and time of administration, kit number, and total dose will be recorded for each administration.

For the Active Comparator treatment, the start date and time, end date and time (or whether the treatment was ongoing), dose per intake and unit, frequency, and form will be recorded.

Listings of study medication administration will be provided separately for the LCM and Active Comparator treatment groups for the SS.

For oral LCM, the date and time of dispensation, amount dispensed, date and time of return, and amount returned will be recorded for each participant and listed for the SS.

8 EFFICACY ANALYSES

Video-EEGs will be assessed locally by the Investigator for assessment of study inclusion, determination of non-severe or severe seizure burden severity at Baseline, any medical decisions or medical interventions. Calculation of seizure burden as a continuous variable will be based solely on the assessment of a central reader.

Note that as study eligibility is determined by the Investigator prior to randomization, it is possible that the Baseline video-EEG data provided by the central reader will not contain any qualifying seizures, or that it will contain less than the 2 minutes of cumulative seizures or 3 identifiable seizures >=10 seconds which are required for study inclusion. If there are no

qualifying seizures on the Baseline video-EEG, none of the efficacy endpoints will be calculated for that participant. Any such participants will therefore be excluded from the FAS and the PPS.

Similarly, Baseline seizure severity (severe, non-severe) is determined by the Investigator at Baseline and is used for randomization stratification. It is possible that the Baseline seizure burden subsequently calculated from the data provided by the central reader does not support the category provided by the Investigator on the eCRF. For all analyses where Baseline seizure burden severity is included as a categorical variable, this will refer to the original classification (used for randomization) from the Investigator.

A listing of video-EEG data provided by the central reader will be provided for the SS and will include the date and time that video-EEG monitoring started, the start date and time and duration of each seizure observed, the start date and time and duration of any interrupted or uninterpretable sections of video-EEG, and the date and time that video-EEG monitoring ended. The dates and times of the start and end of video-EEG monitoring which are provided on the eCRF will not be listed. All derived efficacy endpoints will be listed for the FAS.

The primary efficacy endpoint of this study is the reduction in transformed seizure burden measured in the Evaluation Period video-EEG compared with the Baseline video-EEG; "Evaluation Period" is the 2-hour evaluation for efficacy that will start 1 hour after initiation of randomized treatment (LCM or Active Comparator).

The reduction in seizure burden from Baseline is defined as the difference between the average per hour seizure burden (min/h) at Baseline (calculated over a Baseline Period of up to 2 hours) and the average per hour seizure burden (min/h) calculated over 2 hours after the start of initial study drug treatment divided by the average per hour seizure burden at Baseline and multiplied by 100. This primary efficacy variable is based on the seizure burden (transformed to log [x+1]) measured by the video-EEG at Baseline and during the Evaluation Period as stated above. The transformation log[x+1] is applied to both the seizure burden at Baseline and to the seizure burden in the Evaluation Period before calculating the reduction in seizure burden. The transformation log(x+1) is applied to the seizure burden data to achieve the normal distribution assumption. The lognormal function was reported to adequately simulate the seizure burden time course with the characteristic positive skewness seen in the distribution of seizures over time. It was also reported to achieve a smoothing of any discontinuities in the seizure burden time courses (Stevenson et al. Treatment Trials for Neonatal Seizures).

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Primary efficacy variable

The primary efficacy variable will be analyzed at the end of the study using Bayesian methodology for the FAS and PPS. This will involve utilizing a linear model with treatment, severity (non-severe or severe seizure burden as determined by the Investigator), and Baseline seizure burden (transformed to log [x+1]) 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 the treatment group coefficient and the difference between LCM and Active Comparator will be summarized (using means, SD and 90% credible intervals). The posterior probability that the difference (LCM-Active Comparator) in reduction in

seizure burden is positive (ie, the probability that LCM is better than Active Comparator) will be presented.

Participants who received rescue medication (as defined in Section 6.3.4) in the 3 hours following the first administration of study medication will be excluded from the primary efficacy analysis.

The distribution of the reduction in seizure burden will be evaluated as part of the statistical modelling procedure. If the data are not normally distributed after log transformation, alternative methods of transformation and/or analysis (eg, non-parametric comparison of seizure burden) will be considered.

If the study is stopped for any reason prior to the completion of enrollment (ie, fewer than 32 participants randomized and dosed), the primary efficacy variable will not be analyzed as described above, and therefore no inferential statistics will be displayed in the tables. In this case, the summary tables (for FAS and PPS) will include descriptive statistics only for the absolute seizure burden reduction from Baseline in the Evaluation Period.

8.1.2 Sensitivity analysis of the primary efficacy variable

The following sensitivity analyses will be performed for the FAS:

- The primary efficacy variable will be analyzed by the primary cause of seizure (HIE, hemorrhage, or infarction; CNS malformations; CNS infections; other) and concomitant use of hypothermia for all subgroups with sufficient data available.
  - If the study is stopped prior to the completion of enrollment, this sensitivity analysis will not be performed as planned. In this case, only descriptive statistics for the absolute seizure burden reduction from Baseline in the Evaluation Period will be presented for each subgroup.
- The analysis described in Section 8.1.1 will be repeated with additional covariates for PNA of the study participants, gender, and clinical site (if feasible).
  - If the study is stopped prior to the completion of enrollment, this sensitivity analysis will not be performed.
- The analysis described in Section 8.1.1 will be repeated including study participants (if any) who were administered any rescue medication (as defined in Section 6.3.4) in the 3 hours following the first administration of study medication. The seizure burden for these participants will be imputed as described in Section 8.1.3.
  - If the study is stopped prior to the completion of enrollment, this sensitivity analysis will not be performed as planned. In this case, only descriptive statistics for the absolute seizure burden reduction from Baseline in the Evaluation Period will be presented, including imputed values where applicable.

8.1.3 Primary efficacy variable and rescue medication

Study participants with rescue medications (as defined in Section 6.3.4) introduced in the 3 hours following the first administration of study medication will be excluded from the main analysis.

As a sensitivity analysis, study participants receiving rescue medication in the 3 hours following first dose will be included in the analysis, and the participant's seizure burden (transformed to log [x+1]) values and the reduction in seizure burden will be based on the imputed values as described below.

The seizure burden of any participants with rescue medications in the 3 hours following the first administration of study medication will be imputed based on the worst response for participants without rescue medication.

The imputed values will be based on the Baseline value for the study participant receiving the rescue medication and the minimum value between zero and the minimum calculated percent change between 3 hour Evaluation Period seizure burden (min/h) and Baseline [(Baseline seizure burden – 3 hour Evaluation Period seizure burden)/ Baseline seizure burden x 100%] for all the study participants that did not receive rescue medication. Therefore, the 3-hour Evaluation Period seizure burden activity for the study participant who received rescue medication will be imputed as:

$$\left(1 - min\left(0, min(\boldsymbol{x})\right)/100\right) * b_r$$

Where, b_r is the Baseline value of the study participants who received rescue medication, $\boldsymbol{x} = (\boldsymbol{x_1}, \boldsymbol{x_2}, \ldots, \boldsymbol{x_n})$ is the vector of % changes as calculated above for the n first study participants i.e. $x_i = \frac{b_i - e_i}{b_i} * 100\%$, b_i is the Baseline value for the i^{th} study participant, e_i is the 3 hour Evaluation Period seizure burden for the i^{th} study participant.

The imputed seizure burden will be limited to a maximum value of 60 min/h.

Example:

If we have 32 participants evaluated and participant numbers 13 and 20 received rescue medication, Table 8–1 demonstrates the calculation mentioned above:

Table 8–1: Seizure burden imputation for participants receiving rescue medication

Rescue med	Participant	b	e	x	min(x)	min(0,min(x))	Imputed 'e' for participants with rescue	Final 'e' used in analysis
no	1	3	6	-100				6
no	2	10	11	-10				11
no	3	40	10	75				10
no	4	2	5	-150				5

Table 8–1: Seizure burden imputation for participants receiving rescue medication

Rescue med	Participant	b	e	x	min(x)	min(0,min(x))	Imputed 'e' for participants with rescue	Final 'e' used in analysis
no	5	5	6	-20				6
no	6	8	1	87.5				1
no	7	9	5	44.44444				5
no	8	11	12	-9.09091				12
no	9	22	20	9.090909				20
no	10	25	22	12				22
no	11	30	10	66.66667				10
no	12	4	3	25				3
yes	13	5	4	20			12.5	12.5
no	14	15	14	6.66667				6.66667
no	15	12	15	20				20
no	16	27	22	18.51852				18.51852
no	17	8	12	-50				-50
no	18	19	16	15.78947				15.78947
no	19	11	9	18.18182				18.18182
yes	20	35	31	34.88571			60	60
no	21	10	11	-10				-10
no	22	5	4	20				20
no	23	21	19	9.52381				9.52381
no	24	18	15	16.66667				16.66667
no	25	24	25	-4.16667				-4.16667
no	26	6	4	33.33333				33.33333
no	27	9	6	33.33333				33.33333
no	28	13	12	7.69231				7.69231
no	29	17	18	-5.88235				-5.88235
no	30	20	15	25				25
no	31	10	5	50				50

Table 8–1: Seizure burden imputation for participants receiving rescue medication

Rescue med	Participant	b	e	x	min(x)	min(0,min(x))	Imputed 'e' for participants with rescue	Final 'e' used in analysis
no	32	12	6	50				50
					-150	-150		

8.1.4 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.

The Baseline seizure burden will be calculated as the total duration of seizures (in minutes) between -2 and 0 hours before the first dose of study medication divided by the total duration of interpretable video-EEG (in hours) in the same period.

Similarly, the seizure burden in the Evaluation Period will be calculated as the total duration of seizures between 1 and 3 hours after the first dose of study medication divided by the duration of interpretable video-EEG available in the same period.

Note that in Protocol Amendment 1 the Baseline seizure burden was determined over a period of up to 1 hour prior to the initiation of randomized study medication. In Protocol Amendment 2 the Baseline period for the assessment of seizure burden was extended to a period of up to 2 hours.

For all participants the Baseline seizure burden will be calculated based on the total duration of interpretable video-EEG available in a period up to 2 hours prior to the first dose of randomized study medication regardless of the protocol under which enrolment occurred.

8.2 Statistical analysis of the secondary efficacy variable

All secondary endpoints, listed below, will be summarized descriptively for the FAS.

- Proportion of responders in the Evaluation Period video-EEG compared with the Baseline video-EEG
  - 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
- Proportion of participants with at least 80% reduction in the Evaluation Period video-EEG compared with the Baseline video-EEG
  - The 2-hour evaluation for efficacy is as described above
- Time to response across the 48-hour Treatment Period

- Time to seizure freedom across the 48-hour Treatment Period
- 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 non-severe or severe seizure burden at Baseline
- Categorized percentage reduction in seizure burden in the Evaluation video-EEG compared with the Baseline video-EEG (<-25% [worsening], -25% to <25% [no change], 25% to <50%, 50% to <80%, and ≥80%)

8.2.1 Proportion of responders in the Evaluation compared with Baseline

A responder is defined as a study participant who achieved the following reduction in seizure burden without need for rescue medication, compared with the seizure burden measured during the Baseline Period immediately prior to the study medication 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 by the Investigator as having non-severe seizure burden during Baseline

  OR

- At least 50% reduction of seizure burden in participants who were categorized by the Investigator as having severe seizure burden during Baseline

For the categorization into severe vs non-severe 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 non-severe seizure burden otherwise.

The reduction in seizure burden will be calculated based on the Baseline seizure burden and seizure burden for the Evaluation Period which are calculated as described in Section 8.1.4. No transformation or imputation will be applied to the seizure burden.

The percentage reduction will be calculated as the difference between the seizure burden at Baseline and the seizure burden in the Evaluation, divided by the seizure burden at Baseline and multiplied by 100. No rounding will be applied when calculating percentage reduction, one decimal will be considered for comparison (for example, if the percent change is 79.999%, then consider 1 decimal as 79.9% which is less than 80%).

Study participants will be considered non-responders if they receive rescue medication (as defined in Section 6.3.4) in the 3 hours following the first administration of study medication.

The numerator is defined as the number of responders as described above. The denominator is defined as the number of participants in the FAS.

8.2.2 Proportion of participants with at least 80% reduction

The 80% reduction in seizure burden analysis will be performed as indicated in Section 8.2.1 above for all participants regardless of seizure burden severity.

8.2.3 Time to response across the first 48-hours

Time to response (where response is defined as a reduction in seizure burden from Baseline of at least 80% in participants with non-severe seizure burden, and of at least 50% for participants with severe seizure burden) and time to at least 80% reduction in seizure burden, regardless of severity, will be analyzed across the 48 hours.

The time to reduction in seizure burden is measured in hours, defined as the first time point when the responder criteria (defined in Section 8.2.1) are met minus the date and time of the first dose of randomized study medication administration. Participants will be evaluated for response at the following time points: 3 hours, 8 hours, 16 hours, 24 hours, 32 hours, 40 hours, and 48 hours after the initial drug administered dose. Response will be calculated based on the seizure burden in the last 1 hour prior to the time point, except for the 3 hour time point, which is calculated based on the seizure burden between 1 and 3 hours after the first administration of study medication. If less than 30 minutes of interpretable video-EEG are available in the 1 hour prior to the time point, then response will be calculated based on the seizure burden for the most recent 30 minutes of interpretable video-EEG in the 2 hours (for the 8 and 16 hour time points) or 4 hours (for the 24, 32, 40 and 48 hour time points) prior to the time point. The 30 minutes of video-EEG does not need to be continuous. If 30 minutes of interpretable video-EEG are not available in this extended period then response will be regarded as missing at that time point.

Time to response is censored at the date/time the participant received rescue medication (as defined in Section 6.3.4), or stopped video-EEG monitoring, or otherwise at the end of the 48-hour period. When the time of rescue medication administration is not collected, 23:59 will be used together with the known date. Response will not be determined for time points after the time of censoring, even if sufficient video-EEG is available (eg, if a participant is censored at 15.75 hours after first dose, response will not be determined for the 16 hour time point based on video-EEG between 15 and 15.75 hours after first dose).

The time to response will be presented by treatment group using the Kaplan-Meier survival method. The median time to events and the 95% CI of the median time, and the Kaplan-Meier estimates will be summarized descriptively. Kaplan-Meier plots will also be presented.

8.2.4 Time to seizure freedom across the first 48-hours

Seizure freedom is defined as 0 minutes of seizures in a 1-hour period (or 2-hour period for the 3-hour time point) and will be analyzed across the 48 hours.

The time to seizure freedom is measured in hours, defined as the first time point when the response criterion is met minus the date and time of the first dose of randomized study medication administration. Participants will be evaluated for seizure freedom response at the following time points: 3 hours, 8 hours, 16 hours, 24 hours, 32 hours, 40 hours, and 48 hours after the initial drug administered dose. Seizure freedom will be determined from the last 1 hour prior to the time point, except for the 3 hour time point, which is determined from the period between 1 and 3 hours after the first administration of study medication. If less than 30 minutes of interpretable video-EEG are available in the 1 hour prior to the time point, then response will

be calculated based on the seizure burden for the most recent 30 minutes of interpretable video-EEG in the 2 hours (for the 8 and 16 hour time points) or 4 hours (for the 24, 32, 40 and 48 hour points) prior to the time point. The 30 minutes of video-EEG does not need to be continuous. If 30 minutes of interpretable video-EEG are not available in this extended period then seizure freedom will be regarded as missing at that time point.

Time to response is censored at the date/time the participant received rescue medication (as defined in Section 6.3.4), or stopped video-EEG monitoring, or otherwise at the end of the 48-hour period. When the time of rescue medication administration is not collected, 23:59 will be used. Seizure freedom will not be determined for time points after the time of censoring, even if sufficient video-EEG is available (eg, if a participant is censored at 15.75 hours after first dose, seizure freedom will not be determined for the 16 hour time point based on video-EEG between 15 and 15.75 hours after first dose).

The time to seizure freedom response will be presented by treatment group using the Kaplan-Meier survival method. The median time to events and the 95% CI of the median time, and the Kaplan-Meier estimates will be summarized descriptively. A Kaplan-Meier plot will also be presented.

8.2.5 Absolute reduction in seizure burden across the first 48-hours

The Baseline seizure burden will be calculated as the total duration of seizures (in minutes) between -2 hour and 0 hours before the first dose of study medication divided by the total duration of interpretable video-EEG (in hours) in the same period.

Similarly, the seizure burden in the Evaluation Period will be calculated as the total duration of seizures between 1 hour and 3 hours after the first dose of study medication divided by the duration of interpretable video-EEG available in the same period.

For 8, 16, 24, 32, 40 and 48 hour time points, the seizure burden will be calculated as the total duration of seizures in the hour prior to the time point divided by the duration of interpretable video-EEG available in the same period. If less than 30 minutes of interpretable video-EEG are available in the 1 hour prior to the time point, then response will be calculated based on the seizure burden for the most recent 30 minutes of interpretable video-EEG in the 2 hours (for the 8 and 16 hour time points) or 4 hours (for the 24, 32, 40 and 48 hour points) prior to the time point. The 30 minutes of video-EEG does not need to be continuous. If 30 minutes of interpretable video-EEG is not available in this extended period, then the seizure burden will be missing for that time point.

If a participant receives rescue medication at any time after first dose the seizure burden will be excluded from the summary for all subsequent time points.

No transformation or imputation of the seizure burden will be applied for this secondary analysis.

For the Evaluation Period and the 8, 16, 24, 32, 40 and 48 hour time points, the absolute reduction in seizure burden will be calculated as the seizure burden in the Baseline Period minus the seizure burden at that time point.

8.2.6 Percent reduction in seizure burden across the first 48-hours

The percent reduction in seizure burden for the Evaluation Period and the 8, 16, 24, 32, 40 and 48 hour time points will be calculated as the seizure burden at Baseline minus the seizure burden at the respective time point (as defined in Section 8.2.5), divided by the seizure burden in the Baseline Period, multiplied by 100.

8.2.7 Proportion of responders at the end of the first 48-hours

The proportion of responders at the end of the first 48-hours of the Treatment Period is defined similarly to the proportion of responders in the Evaluation Period (as described in Section 8.2.1). The denominator for the percentages will be based on the number of participants with video-EEG data available at the 48 hour time point. The seizure burden between 47 and 48 hours after the start of the Treatment Period will be compared with the seizure burden for the 1-hour Baseline Period.

If less than 30 minutes of interpretable video-EEG are available between 47 and 48 hours after first dose then the response will be determined based on the seizure burden for the most recent 30 minutes of interpretable video-EEG between 44 and 48 hours after the start of the Treatment Period. The 30 minutes of video-EEG does not need to be continuous. If less than 30 minutes of interpretable video-EEG are available between 44 and 48 hours after first dose then response at 48 hours will be regarded as missing.

Participants who receive rescue medication (as defined in Section 6.3.4) at any time between 0 and 48 hours after the first administration of study medication will be regarded as non-responders.

8.2.8 Proportion of study participants who are seizure free at 24-hours

For the study participants with severe seizure burden at Baseline (as determined by the Investigator), the numerator is defined as the number of participants with severe seizure burden at Baseline who had no seizures between 23 and 24 hours after the start of the Treatment Period. The denominator for the percentages will be based on the number of participants with video-EEG data available at the 24 hour time point.

If less than 30 minutes of interpretable video-EEG are available between 23 and 24 hours after first dose then the response will be determined based on the seizure burden for the most recent 30 minutes of interpretable video-EEG between 20 and 24 hours after the start of the Treatment Period. The 30 minutes of video-EEG does not need to be continuous. If less than 30 minutes of interpretable video-EEG are available between 20 and 24 hours after first dose then seizure freedom at 24 hours will be regarded as missing.

Participants who took rescue medication (as defined in Section 6.3.4) at any time between first dose and 24-hours after first dose will be regarded as not seizure free.

The proportion of study participants who are seizure free at 24-hours after the start of the study is defined similarly for the participants with non-severe seizure burden at Baseline.

8.2.9 Categorized percent reduction in seizure burden

The categorized percent reduction in seizure burden for the Evaluation Period and over the 48-hour Period (8, 16, 24, 32, 40 and 48 hours) will be defined based on the seizure burden percent reduction from Baseline calculated as described in Section 8.2.6 above.

Participants will be classified in one of the following categories based on their percent reduction from Baseline to the Evaluation Period and across the 48-hour Period: < -25%, -25% to <25%, 25% to <50%, 50% to <80%, and ≥80%.

The number and percentage of participants in each response category will be presented by treatment group for the Evaluation Period and across the 48-hour period. If a participant receives rescue medication at any time after first dose the percent reduction in seizure burden will be excluded from the summary for all subsequent time points.

9 PHARMACOKINETICS

The PK data, along with the safety data collected will be reviewed by the DMC. In addition, serum concentrations of LCM will be monitored and subjected to interpretation on an ongoing basis. The analysis of the PK parameters will include a sub-analysis for any concomitant use of hypothermia if allowed by the available data.

9.1 Pharmacokinetics

Pharmacokinetics summary tables and listings for LCM concentrations will be produced on PK-PPS.

Summary descriptive statistics (geometric mean and CI, geometric CV, mean, SD, median, minimum, and maximum) of serum concentrations will be derived for each time window (30 to 90 minutes after the start of the first infusion, 6 to 8 hours after the start of the first infusion, 30 to 90 minutes after the start of the second or third infusion, 6 to 8 hours after the start of the second or third infusion, day 2, day 3 and day 4). Samples collected outside of the allowed window will be excluded from the analysis and included in listings only. For the day 2, day 3 and day 4 samples, the summary will include only trough concentrations, the allowable window is 6 to 8 hours after the last infusion. If dosing is interrupted for more than 24 hours during the Treatment Period (ie, the time elapsed between the start date/time of any 2 consecutive LCM doses is >24 hours), any PK samples collected at any time after the first 24 hours of the interruption will be flagged on the listing and excluded from the summary. For the purposes of the summary, values below the limit of quantification will be replaced with a value equal to half the limit of quantification.

Serum concentrations of LCM together with demographic and other variables, will be introduced in a PK model. This population PK analysis will be described in a separate analysis plan and reported separately.

10 SAFETY ANALYSES

All safety analyses and descriptive summaries will be presented by treatment group and overall for the SS unless otherwise stated.

- AEs
- SAEs
- neurological examination assessments
- laboratory results

- vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], respiration rate, pulse rate, temperature, and oxygen saturation)
- 12-lead ECG abnormalities
- body weight and length
- head circumference
- Sarnat scale

The following participant characteristics related to safety will also be listed:

- physical examination abnormalities
- cooling status variables (target low body temperature, age since birth when cooling began, duration of cooling [date and start and stop time of cooling], and timing of cooling in relation to first dose of LCM)
- rewarming status variables (duration of rewarming [date and start and stop time of rewarming] and timing of rewarming in relation to first dose of LCM)
- the mother's use of AEDs (including BZD and opiates) at childbirth

10.1 Extent of exposure

Study medication duration will be calculated for the on-treatment phase as defined in Section 3.2.2.5.

This will be calculated as the date of last dose on the Study Termination eCRF minus the start date and time of the first administration of study medication, in hours. The time of the last dose of study medication will be obtained as described in Section 4.2.4.

If the date of the last administration of study medication is partial or missing on the Study Termination eCRF this will be handled as described in Section 4.2.4.

Study medication duration (in hours) will be summarized by treatment group using descriptive statistics.

All summaries will be based on the SS.

A listing of study medication duration will be provided for the SS.

10.2 Adverse events

Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset on or after the start date and time of initial study medication administration.

An overall summary of AEs will be provided. The table will include:

- the numbers and percentage of participants with at least one TEAE
- the number and percentage of participants with any serious TEAEs
- the number and percentage of participants with any non-serious TEAEs
- the number and percentage of participants with any TEAE that led to permanent discontinuation of study medication

- the number and percentage of participants with any drug-related TEAE
- the number and percentage of participants with any severe TEAE
- the number and percentage of participants with any AE leading to death (based on the All Participants Screened Set)
- the number and percentage of participants with any TEAEs leading to death

The following summary tables of TEAEs will be provided by primary SOC and PT. Summaries will be presented by treatment group for the SS.

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs by maximum intensity
  Each participant will be counted at most once per primary SOC or PT according to the maximum intensity of all AEs within that SOC or PT.
- Incidence of drug-related TEAEs
  Drug-related AEs are AEs for which the relationship to study medication is Related.
- Incidence of serious TEAEs by relationship
- Incidence of fatal TEAEs by relationship
- Incidence of TEAEs leading to permanent discontinuation of study medication
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants in any treatment group
- Incidence of TEAEs of special interest

A glossary of all AEs and a listing of all AEs will be provided, based on the All Participants Screened Set. In addition to the data collected on the eCRF, the listing will include the AE duration in days, which will be calculated as the date of AE outcome minus the date of AE onset +1. Duration will not be calculated for AEs with a missing or partial date of onset or date of outcome. The listing will also include the treatment phase at the onset of each AE.

10.3 Clinical laboratory evaluations

10.3.1 Hematology and chemistry parameters

Clinical laboratory parameters are listed in Section 12.1. Continuous laboratory variables summary statistics of observed values and change from Baseline will be presented by treatment group at each time point.

Any laboratory values reported as <xx or >xx in the database will be imputed as the value of xx for the purpose of summaries. The original value will be reported in the listing.

The number and percentage of participants with treatment-emergent markedly abnormal (TEMA) values, TEMA low values, and TEMA high values at each time point and overall will be summarized by treatment group. The overall summary will include scheduled, unscheduled and Early Withdrawal assessments. TEMA criteria are included in the Appendices in

Section 12.2. A laboratory value is regarded as TEMA if the value meets the criteria at a post-Baseline time point and if the participant's Baseline value does not meet the criteria.

The following listings will be provided:

- all laboratory results of clinical chemistry and hematology laboratory tests.
- a separate participant data listing for TEMA (all laboratory assessments for participants with any TEMA values will be included in the listing),

10.3.2 Potential drug-induced liver Injury

A summary of the number and percentage of participants with elevated liver function tests at any point will be summarized overall, and by treatment group for the SS. Scheduled, unscheduled and Early Withdrawal assessments will be included in the summary.

The number and percentage of participants with potential hepatotoxicity with and without symptoms potentially associated with hepatitis or hypersensitivity, and the number and percentage of participants meeting laboratory criteria for potential drug-induced liver injury (PDILI) will be summarized overall and by treatment group for the SS.

Liver function laboratory results for participants with one or more elevated liver function tests will be listed. The listing will include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin and nR. The listing will also indicate whether the participant met the criteria for Hy's Law and whether symptoms of hepatitis and hypersensitivity were present. Criteria for elevated liver function tests, PDILI and Hy's Law are provided in Appendix 12.3. The nR is calculated as the ratio of ALT or AST (whichever is higher) divided by ALP, where ALT, AST and ALP are expressed as multiples of their upper limits of normal (ULN).

Any other laboratory tests performed for PDILI (eg, international normalized ratio [INR] and direct bilirubin) will be included in the listings for hematology and/or clinical chemistry as appropriate.

All PDILI events require immediate action, testing, and monitoring. The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the study medication include but are not limited to those listed in laboratory measurements.

Medical history, blood samples for PK and vital signs collected for PDILI events will be included on the standard listings. Further listings, based on the SS, will be provided for family medical history and most recent study medication administration, including the presence of potentially hepato-toxic medications.

10.4 Vital signs, physical findings, and other observations related to safety

Vital signs SBP, DBP, respiration rate, pulse rate, temperature and oxygen saturation are assessed throughout the study. 12-lead ECG, physical examination and neurological examination abnormalities and biometric parameters are also recorded. Physical and neurological assessments include the Sarnat scale for participants with HIE.

10.4.1 Vital signs

Observed values and changes from Baseline for SBP, DBP, respiration rate, pulse rate, temperature and oxygen saturation will be summarized at each time point.

Temperature will also be summarized by treatment group at each time point separately for participants with concomitant hypothermia treatment and those without concomitant hypothermia treatment (as defined in Section 4.8).

The numbers and percentages of participants with a TEMA value, TEMA low values, and TEMA high values at each time point and overall will be summarized for pulse rate, SBP, DBP and respiration rate by treatment group. The overall summary will include TEMA values from scheduled, unscheduled and Early Withdrawal assessments. TEMA criteria are based on Food and Drug Administration (FDA) Division of Neuropharmacological Drug Products guidelines with some UCB-defined additions and are included in the Appendices in Section 12.2. A vital signs value is regarded as TEMA if the value meets the criteria at a post-Baseline time point and if the participant's Baseline value does not meet the criteria.

A listing of vital signs will be provided for the SS.

10.4.2 12-Lead electrocardiogram

In Protocol Amendment 1, ECGs were scheduled at Baseline and at 0, 3, 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88 and 96 hours during the Treatment Period for participants randomized to LCM. Assessments were to be performed after the LCM infusion. For participants randomized to Active Comparator, assessments were planned at the same time points if these coincided with administration of study medication.

In Protocol Amendment 2, the ECG assessment schedule was revised such that ECGs were planned at Screening (-24 to 0 hours), 1 to 6 hours, 48, and 96 hours during the Treatment Period for participants randomized to LCM. For participants randomized to Active Comparator only the Screening assessment was required.

No changes were made to the schedule of assessments for the Extension Period. In both treatment groups assessments were planned each week of the Extension Period and finally at the SFU visit.

A summary of the number of participants with normal, abnormal not clinically significant, and abnormal clinically significant 12-lead ECG interpretations at each scheduled visit (as reported on the ECG Interpretation eCRF) will be provided for the SS.

A listing of 12-lead ECG interpretations will be provided for the SS.

10.4.3 Physical and neurological examination

A listing of physical examination abnormalities in the Baseline Period will be provided for the SS. Clinically significant physical examination abnormalities during the Treatment, Extension and SFU Periods will be reported as AEs and included in the summaries described in Section 10.2.

A summary of shift from Baseline in each of the 14 components of the neurological examination (classified as normal, abnormal not clinically significant or abnormal clinically significant) at 24 hours, 48 hours, 72 hours and 96 hours will be provided for the SS.

A listing of neurological examination results will be provided for the SS.

10.4.4 Hypothermia treatment

A listing of hypothermia treatment will be provided for the SS by treatment group. This will include the age since birth when cooling began, target low body temperature, date and time cooling began, date and time cooling ended, timing of cooling in relation to first drug dose (in hours, relative day and time), date and time rewarming began, date and time rewarming ended, and timing of rewarming in relation to first dose of study drug (in hours, relative day and time).

10.4.5 Mother's use of AEDs

A listing of mother's use of AEDs (including BZDs and/or opiates) with the information on mother taking AEDs (BZDs and/or opiates) at the time of delivery, medication start date and time, taken medication, and dose per intake will be provided for the SS.

10.4.6 Sarnat scale

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. A listing of Sarnat scale will be provided.

10.4.7 Biometric parameters

Biometric parameters are body length, body weight and head circumference. Observed values and changes from Baseline in biometric parameters will be summarized for post-Baseline visits and time points by treatment group. A listing of biometric parameters will be provided for the SS.

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12 APPENDICES

12.1 Laboratory parameters

Table 12–1: Laboratory parameters

Hematology	Clinical Chemistry
Platelet Count	BUN[a]
RBC Count	Creatinine[b]
Hemoglobin	Glucose
Hematocrit	Potassium
MCV	Sodium
MCH	Calcium
%Reticulocytes	AST
WBC Count	ALT
Neutrophils	ALP
Lymphocytes	Total and direct bilirubin
Monocytes	Total protein
Eosinophils	
Basophils	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume ; RBC=red blood cell; WBC=white blood cell.

[a] Urea or BUN to be tested depending on the local lab´s standard panel for neonates.

[b] During the first days of life, creatinine will only be collected if the site assesses this parameter per standard of care.

12.2 Treatment-emergent markedly abnormal criteria (TEMA) for neonates (postnatal age up to 1 month)

Introduction

This document defines rules to be applied in the safety analyses of the UCB Pharma, Inc. clinical development programs in CNS Therapeutic Area. Rules for detecting treatment-emergent markedly abnormal laboratory values, vital signs, and ECG parameters are considered. The purpose of this document is to bring consistency to reviewing laboratory data without over-riding the Investigator's clinical assessment of these parameters within the clinical context of the study participant.

These TEMA values are based on grade 2 toxicity if appropriate grading is available for age group, based on abnormal values or clinical experience based on discussion with Professor John van den Anker (JA) on 26 February 2018 and 21 March 2018 (see comments).

Table 12–2: Blood pressure/vital signs

Parameter	Low	High	Comment
Pulse rate (heart rate)	<100	>200	Normal range neonates 85-205 [a] Grade 2 is defined as Asymptomatic or symptomatic increase or decrease in heart rate, responsive to medical therapy[b]. Values adapted based on discussion with JA.
Respiration rate	<30	>60	Normal range neonates 30-60 [a] Grade 2 is considered persistent tachypnea and/or hypoxemia requiring high FiO_2 supplementation or CPAP. Associated with other clinical symptoms (nasal flaring, grunting, retractions, pallor, or cyanosis) [b]
SBP mmHg	<40	>100	Normal range preterm day 1-7: 48-63 mmHg; term day 1-week 4: 61-95 mmHg[c] Grade 2 is considered symptomatic and persistent decrease in systolic or mean arterial blood pressure ≥15 mm Hg below normal for age and gender (symptomatic and persistent increase of >= 35 mmHg above normal and gender)[b] Per discussion with JA SBP below 48 mmHg may occur in preterm infants therefore 40 was chosen.
DBP mmHg	<20	n/a	Normal range preterm day 1-7: 25-35 mmHg; term day 1-week 4: 30-55 mmHg[c] Per JA DBP <20 would be clinically meaningful. Usually clinical decisions in this setting are made based on MAP rather than systolic and diastolic pressure

DBP=diastolic blood pressure, SBP=systolic blood pressure.

[a] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X

[b] Munoz et al.; Assessment of Safety in Newborns of Mothers Participating in Clinical Trials of Vaccines Administered During Pregnancy; Clinical Infectious Disease 2014; Table 1: Recommended core dataset of AE definitions and Severity grading

[c] Blood pressure disorders - Victorian Agency for Health Information, Safer Care Victoria on https://www.bettersafercare.vic.gov.au/resources/clinical-guidance/maternity-and-newborn-clinical-network/blood-pressure-disorders#goto-normal-neonatal-blood-pressure-values

Table 12–3: Hematology parameters

Parameter	PNA (days)	Low	High	Comment
WBC count[a] cells/mm3	≤ 7	<5500	>50000	Grade 2 tox criteria[b] No criteria defined for high WBC; definition based on discussion with JA
	>7	<2000		
Neutrophils[a] cells/mm3	≤ 1	<2000	n/a	Grade 2 tox criteria[b] No criteria defined for high neutrophils count Adapted based on discussion with JA
	>1	<1000		

Table 12–3: Hematology parameters

Parameter	PNA (days)	Low	High	Comment
Platelets[a] cells/mm3 (10^9/L)		<100000 (100)	>1000000 (1000)	Grade 2 tox criteria[b] No criteria defined for high platelets count; definition based on discussion with JA
Hemoglobin[a] g/dL, (mmol/L)	≤ 7	<13 (<8.05)	> 16 g/dl	Grade 2 tox criteria[b] No criteria defined for high hemoglobin. DMID criteria are more stringent[c] High Hb cutoff added per JA
	8-≤21	<11 (<6.81)	n/a	
	22-35	<9.5 (<5.88)		

[a] All parameters will be presented in SI units in tables and listings

[b] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf[c] DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007 DRAFT

Table 12–4: Chemistry (without Bilirubin)

Parameter	PNA (days)	Low	High	Comment
Calcium mg/dL (mmol/L)	<7	<6.5 (<1.63)	>=12.4 (>=3.1)	Grade 2 toxicity based on DAIDS criteria[a]
	>=7	<7.8 (<1.95)	>=11.5 (>=2.88)	
Potassium mEq/L (mmol/L)		<3.0	>6.0	Grade 2 toxicity based on DAIDS criteria[a]
Sodium mEq/L (mmol/L)		<130	>=150	Grade 2 toxicity based on DAIDS criteria[a]
Glucose mg/dl (mmol/L)		<50 (<2.78)	>160 (>8.89)	Grade 2 toxicity based on DAIDS criteria[a]
AST/ALT/ALP		n/a	>2.5 ULN	Grade 2 toxicity based on DAIDS criteria[a]

[a] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Table 12–5: Chemistry (Bilirubin)

PNA (hours)	Bilirubin (High) mg/dl		Comment
	Gestational Age <38 weeks	Gestational Age >=38 weeks	
≤12	6	8	Considered PCST if bilirubin values reach cutoff for phototherapy recommendation, considering neonates with risk factors Based on AAP guideline 2004[a]
>12 and ≤ 24	8	10	
>24 and ≤ 48	11	13	
>48 and ≤ 72	13	15	
>72 and ≤ 96	14	17	
> 96	15	18	

[a] Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, AAP, PEDIATRICS Vol. 114 No. 1 July 2004

12.3 PDILI

Table 12–6: Elevated liver function tests and Hy's Law criteria

Parameter	Criteria
ALT	>3 x ULN >5 x ULN >8 x ULN >10 x ULN >20 x ULN
AST	>3 x ULN >5 x ULN >8 x ULN >10 x ULN >20 x ULN
ALT or AST	>3 x ULN >5 x ULN >8 x ULN >10 x ULN >20 x ULN
Total bilirubin	>1.5 x ULN >2 x ULN
ALP	>1.5 x ULN

Parameter	Criteria
PDILI	(AST or ALT ≥ 3 x ULN) and total bilirubin ≥ 1.5 x ULN at the same visit (AST or ALT ≥ 3 x ULN) and total bilirubin ≥ 2 x ULN at the same visit
Hy's law	(AST or ALT ≥ 3 x ULN) and total bilirubin ≥ 2 x ULN and ALP < 2 x ULN at the same visit

13 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

13.1 Amendment 1

The following changes were made to reflect updates made in Protocol Amendment 1:

- Four new efficacy endpoints were added
- The end time of video-EEG was updated from 96 hours after the first dose of study medication to 48 hours after the first dose of study medication
- The response adaptive randomization scheme was replaced with a simple 1:1 randomization stratified by seizure severity at Baseline
- The imputation of the seizure burden for the primary efficacy variable for participant with rescue medication was updated based on the change to the randomization scheme and moved to the efficacy section as a sensitivity analysis
- The primary efficacy analysis will now exclude participants who used rescue medication in the 3 hours following first administration of study medication.
- The summary of Thompson scores was removed

The following additional updates were made:

- Further details of the Early Withdrawal and Extension Period visit mapping procedure were added
- The definition of completed study was updated to specific that the SFU visit must also be attended
- An All Participants Screened Set was defined for disposition outputs
- A list of changes to the protocol-defined analysis was added
- A summary and listing of Active Comparator treatments was added
- A listing of rescreened participants was added
- A summary of baseline characteristics was added
- Further detail on imputation of partial dates and times for concomitant medication, AEs and date of last study medication administration was added
- Primary cause of seizure subgroups were updated to be grouped together as per the protocol
- A definition of concomitant hypothermia treatment was added
- The disposition summary was simplified
- The listing of prior non-AED medications was removed
- A listing of drug accountability was added
- A listing of video-EEG data from the central reader was added
- Further detail of seizure burden calculation was added

- The derivation of secondary efficacy variables was updated so that if there is insufficient interpretable video-EEG available in the hour prior to a given time point, the endpoints can be calculated using video-EEG data from the 2 hours prior to the time point (for the 8 and 12 hour time points) or the 4 hours prior to the time point (for the 24, 32, 40 and 48 hour time points)
- Study medication duration was updated so that the dosing interval is no longer added to the time after the last dose of study medication
- Selected safety outputs (overview of TEAEs and incidence of TEAEs) summarized by the primary cause of seizure subgroup were added as per the protocol
- The summaries of non-serious TEAEs, non-serious TEAEs by relationship, drug-related serious TEAEs, and TEAEs by relationship were removed
- PDILI outputs were updated to align with the latest UCB standards and to include two new figures
- Details of summaries for 12-lead ECG, physical examination and neurological examination were added
- Post-Baseline visits were removed from the summary of the Sarnat Scale as these will not be collected according to the Protocol
- The list of optional laboratory parameters was removed from the appendices as these will not be collected according to the Protocol
- Additional detail and clarification was added throughout, where deemed appropriate to describe the analysis and presentations required

13.2 Amendment 2

The following updates were made in SAP Amendment 2:

- Global updates were made to take into account the changes as a result of Protocol Amendment 2. These were mainly to the following:
  - Inclusion criteria for age
  - Duration of the Baseline video-EEG
- Section 3.2.2.5 was added to define how events and procedures are assigned to the pre-treatment, on-treatment, and post-treatment phases for analysis purposes.
- Section 3.2.3 was updated to clarify that unscheduled assessments will be included in the descriptive statistics if designated as the Baseline assessment. In addition, the windows for the Extension Period visits were updated to be based on 7 days after the end of the Treatment Period. This section was further updated to clarify the mapping of assessments performed at the Early Withdrawal visit for participants enrolled under Protocol Amendment 2.
- The definition of completed study was updated in Section 3.2.5 to be based on the Study Termination eCRF only.
- Section 3.4.3 was updated to clarify that participants with no qualifying seizures on the Baseline video-EEG will be excluded from the FAS.

- Section 4.2.1 was updated to include imputation of missing start times for concomitant medications which is needed for the determination of rescue medication use during the Treatment Period. Minor updates were made to the imputation of missing start dates to handle partial end dates.
- Minor updates were made to Section 4.2.2 for imputation of missing AE onset dates.
- In Section 5.1 the summary of participant disposition was amended to remove the rows for completing the Treatment Period and entering the Extension Period. A new row was added to summarize the number of participants Completing 48 hours of video-EEG.
- Section 6.1 was updated to present the gestational age in weeks to 1 decimal place. In addition, the summaries based on the PPS were removed.
- In Section 6.3.1 the definition of prior medication was updated to include medications that started prior to the first dose of randomized study medication rather than prior to the date of ICF. In addition, in Section 6.3.3 a new definition was added for follow-up medications. These changes were made in order to ensure that all medications could be classified as prior, concomitant, and/or follow-up.
- Section 8 was updated to clarify that participants without any qualifying seizures on the Baseline video-EEG will be excluded from the FAS and the PPS.
- Section 8.1.1 was updated to clarify that in the event that the data are not normally distributed after transformation then alternative methods may be performed.
- Section 8.1.4 was updated to clarify that the Baseline seizure burden will be calculated based on up to 2 hours of video-EEG for all participants, regardless of the protocol version under which enrolment occurred.
- Section 8.2.9 was updated to clarify that for any participant receiving rescue medication at any time after first dose the percent reduction in seizure burden will be excluded from the summary for all subsequent time points.
- Section 9.1 was updated to clarify that the time between consecutive doses should be based on the start date and time of each dose of LCM, for the evaluation of dosing interruptions.
- Section 10.1 was updated to clarify that the study medication duration will be calculated for the on-treatment phase only.
- The categorical summary of the number of LCM doses received was removed from Section 10.1. The summary of cumulative study medication duration was also removed.
- Section 10.2 was updated to remove summaries by Treatment Period, Extension Period and SFU.
- Section 10.2 was updated to remove the summaries of AEs by primary cause of seizure subgroups as these were not anticipated to be clinically meaningful on a small number of participants in each subgroup. The change to the planned analysis section (Section 3.8) was updated accordingly. Section 10.2 was also updated to remove the following summary tables of AEs/TEAEs:
  - Incidence of pre-treatment AEs

- Incidence of TEAEs leading to death
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants by relationship

Additionally, the participant summaries for incidence of serious TEAE, TEAEs leading to permanent discontinuation of study medication, and TEAEs of special interest have also been removed.

- Sections 10.3.1 and 10.4.1 were updated to clarify the definition of TEMA for laboratory tests and vital signs assessments.
- Section 10.3.1 was updated to remove the summaries of participant numbers experiencing TEMA values as this information is presented in corresponding listings.
- Section 10.3.2 was updated to remove the figures for the evaluation of PDILI events.
- Section 10.4.1 was updated to remove the summaries of participant numbers experiencing TEMA values as this information is presented in corresponding listings. In addition, the figures were removed.
- Section 10.4.2 was updated to clarify the different time points for the ECG assessments in Protocol Amendment 1 and Protocol Amendment 2.
- Section 10.4.6 was updated to remove the summary of the Sarnat scale. This data will be listed only.
- The Thompson score was removed from the SAP throughout as this was no longer applicable under the amended protocols. No participants were enrolled under the original protocol therefore no Thompson score data was collected.
- An error in the TEMA criteria for platelets was corrected.

Additional minor clarifications and cosmetic updates were made throughout.

13.3 Amendment 3

The following updates were made in SAP Amendment 3:

- The number of significant figures/decimal places for the PK concentrations and the corresponding summary statistics and the number of decimal places for the 90% credible intervals, 95% CIs, and the posterior probability were clarified in Section 3.1.
- Section 3.5 was updated to clarify that participants will be summarized according to the actual/received treatment for the All Participants Screened Set as well as the SS and PK-PPS.
- In Section 5.1, study participants completing 30 minutes of video-EEG in the Evaluation Period was added to the disposition and discontinuation reasons summary, a listing of the planned (randomized) and actual treatment was added, and the mean initial dose in the Active Comparator treatment summary was removed.

- Section 6.3 was updated to remove reference to the reported indication when flagging AEDs and to clarify that the classification of AEDs will be confirmed by the Study Physician prior to database lock.
- Sections 6.3.2 and 6.3.3 were updated to clarify that time is used in the classification of concomitant and follow up medications, where available.
- Sections 8.1.1 and 8.1.2 were updated to clarify which analyses will be performed if the study is stopped prior to the completion of enrollment.
- The denominator used for the calculation of percentages was clarified in Sections 8.2.7 and 8.2.8.
- The time windows of the PK samples were clarified in Section 9.1

Additional minor clarifications were made throughout.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

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