STATISTICAL ANALYSIS PLAN

Study: EP0151

Product: Lacosamide

A MULTICENTER, OPEN-LABEL, FOLLOW-UP STUDY TO ASSESS THE LONG-TERM USE OF ORAL LACOSAMIDE IN STUDY PARTICIPANTS WHO COMPLETED EP0034 OR SP848 AND RECEIVED LACOSAMIDE TREATMENT

LONG-TERM USE OF ORAL LACOSAMIDE IN PEDIATRIC STUDY PARTICIPANTS WITH EPILEPSY

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Confidentiality Statement

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study EP0151 is based on the protocol dated 13 Apr 2020.

SAP Version	Approval Date	Change	Rationale
1	<DD Mmm YYYY>	Not Applicable	Original version

LIST OF ABBREVIATIONS

List of Abbreviations

AE	Adverse Event
AED	Antiepileptic Drug
BMI	Body Mass Index
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ETV	Early Termination Visit
LCM	Lacosamide
MA	Markedly Abnormal
MedDRA	Medical Dictionary for Regulatory Activities
PDILI	Potential Drug-Induced Liver Injury
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
VNS	Vagus Nerve Stimulation

List of Abbreviations

WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report for EP0151.

1.1 Objectives and Estimands/Endpoints

Table 1–1: Objectives and Estimands/Endpoints

Objectives	Endpoints
Primary	
Primary Objective: To assess the long-term use of Lacosamide (LCM) oral solution dosed at 2mg/kg/day to 12mg/kg/day when administered to pediatric study participants with epilepsy who have completed EP0034 or SP848	Primary Endpoints: • Treatment-emergent adverse events (TEAEs) reported by the study participant or caregiver or observed by the Investigator • Withdrawals from study due to TEAEs • Withdrawals from study due to Serious adverse events (SAEs) • Modal daily dose (mg/kg/day) • Maximum daily dose (mg/kg/day)

1.2 Study design

EP0151 is a multi-center, long-term, open-label, follow-up study to assess the long-term use of LCM oral solution (a formulation suitable for administration to children; also referred to as syrup) for pediatric study participants <6 years of age with epilepsy who have completed either EP0034 or SP848.

Study participants who complete EP0034 or SP848 will be offered participation in EP0151 and will have access to open-label follow-up treatment with LCM. Approximately 80 to 100 study participants are estimated to be eligible for enrollment.

Visit 1 for EP0151 will be the same as Visit 13 in EP0034 or SP848. Clinic visits will be scheduled approximately every 26 weeks relative to the EP0151 Visit 1 date. A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits.

All study participants in EP0151 will receive LCM. The Investigator may maintain the study participant's LCM dose from previous studies EP0034 or SP848, decrease the dose in decrements of 2mg/kg/day per week to a minimum dose of LCM 2mg/kg/day, or increase the dose in increments of 2mg/kg/day per week up to a maximum dose of LCM 12mg/kg/day or 600mg/day, whichever is lower, administered twice per day (BID).

This study involves a Treatment Period of approximately up to 205 weeks, depending on the age of the study participant, and an End of Study Period of approximately 8 weeks (including a

Taper Period and a Safety Follow-Up Period). Study participants who reach the end of the study and choose to continue treatment with LCM may be immediately prescribed LCM. The Termination Visit at the end of the Treatment Period will be the last study visit completed for study participants who continue treatment with prescribed LCM. Study participants who choose not to continue with LCM treatment and who are taking a dose of 3mg/kg/day or higher will enter an End of Study Period following completion of the Termination Visit or Early Termination Visit, and will gradually taper from LCM treatment during the Taper Period; a Final Visit will be conducted 30 days after the final dose of LCM.

In situations where provision of LCM oral solution in certain participants >6 years of age (eg, developmental delay, need for more precise dosing as afforded by oral solution formulation, etc.) who may need a longer period of treatment with LCM oral solution, the situation will be assessed for approval by UCB on a case-by-case basis following discussions with the participant's physician.

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

2 STATISTICAL HYPOTHESES

No statistical hypotheses testing will be conducted in this study.

3 SAMPLE SIZE DETERMINATION

No formal sample size calculations have been performed for this study, as there are no statistical hypotheses being tested. The sample size will be determined by the number of participants in EP0034 or SP848 who have been treated with LCM that are eligible to enter this open-label follow-up study. Approximately 80 to 100 study participants are estimated to be eligible for enrollment.

4 POPULATIONS FOR ANALYSIS

The Safety Set (SS) will consist of all study participants who sign an informed consent form (ICF), and take at least 1 dose of study medication in this study. This analysis set will be used for all safety analyses.

5 STATISTICAL ANALYSES

5.1 General Considerations

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. The denominator for percentages will be based on the number of participants appropriate for the purpose of analysis. Unless otherwise noted, all percentages 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%. 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 value

All summaries, unless otherwise stated below, will be presented overall for all participants and additionally based on the participant's age at time of entry into study EP0151, using the following age groups:

- ≥2 to <4 years
- ≥4 to <6 years

All summaries will be descriptive; no statistical hypothesis testing is planned.

Only scheduled visits will be included in summaries. A complete set of listings containing all documented data including scheduled and unscheduled and all calculated data (eg, change from Baseline) will be generated, and will be sorted by site, participant number and visit (where applicable). Study participant numbers that were utilized in SP848 and EP0034 will continue to be used in EP0151.

5.1.1 Handling of missing data

5.1.1.1 Missing data

No imputation of missing values for analysis parameters is planned unless otherwise noted. Imputations for missing or partial values for dates for adverse events (AEs) and medications will be applied to determine if they are to be considered treatment-emergent or concomitant, respectively.

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to LCM per the investigator will be assumed to be related. Incomplete or missing dates for events will be handled as described in Section 5.1.1.2.

5.1.1.2 Incomplete dates for adverse events and concomitant medications

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication

will be displayed as reported in the participant data listings (ie, no imputed values will be displayed in data listings).

- Missing start day, but month and year present:

  If the start of LCM occurred in the same month and year as the occurrence of the AE/concomitant medication, the start day of the event/concomitant medication will be assigned to the day of first intake of LCM. Otherwise the start day will be set to the 1st day of the month.

- Missing start day and month, but year present:

  If the start of LCM occurred in the same year as the occurrence of the AE/concomitant medication, the start day and month will be assigned to the date of first intake of LCM. Otherwise the start day and month will be set to January 1st.

- Missing end day, but month and year present:

  The end day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to the latest of the date of Final Visit or the date equivalent to 30 days after last intake of LCM.

However, if the Final Visit year and year for the date which is 30 days after last intake of LCM are greater than the event/concomitant medication year, the day and month are to be set to December 31st.

5.1.1.3 Definition of concomitant medication in case of missing dates

With respect to definition of medication as concomitant, the following rule will be applied in case of completely missing stop and/or start date information:

Medications with a missing start date whose stop date is either unknown or after the date of the first dose of LCM will be considered as concomitant medication. Medications with missing start date whose stop date is prior to first intake of LCM will not be considered concomitant.

In participant data listings, dates will be displayed as reported.

5.1.1.4 Incomplete dates for the last administration of LCM

For purposes of imputing missing components of partially reported dates for the last administration of LCM, the algorithms listed below will be followed. Stop dates of LCM will be displayed as reported in the participant data listings (ie, no imputed values will be displayed in data listing).

- Missing last administration day, but month and year present:

  The last administration day will be set to the last day of the month or the date of the final contact, whichever is earlier in the month.

- Missing last administration day and month, but year present:

  The last administration day will be set to the last day of the year or the date of the final contact, whichever is earlier in the year.

- Completely missing date of last administration:

  For calculating the duration of exposure, if the date of last administration is completely missing and no information could be obtained from data cleaning exercises, the date of last administration should be imputed as the date of last contact according to the Study Termination eCRF module. For all other purposes, no imputation will be done if the date of last administration is completely missing.

If a participant died during the study, and the imputed last administration date according to the rules above is after the date of death, the last administration date will be assigned to the date of death.

5.1.1.5 General imputation rule for incomplete dates

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of AEs
- Start and stop dates of concomitant medication
- Start and stop dates of LCM

Completely missing dates will not be replaced and the corresponding derived variables will be set to missing.

5.1.2 General study level definitions

5.1.2.1 Analysis Time Points

5.1.2.1.1 First and last dose of LCM

Unless otherwise noted, all references to the first dose of LCM in this SAP refer to the first dose of LCM during EP0151 (ie, not the first dose of LCM from the previous study in which participants participated prior to EP0151). Unless otherwise noted, all references to the last dose of LCM in this SAP refer to the last dose of LCM in EP0151.

5.1.2.1.2 Relative day

Relative day will be calculated as the current date minus the date of first dose of LCM plus 1 for days on or after the day of first dose of LCM and prior to or on the day of last LCM dose (e.g., the day of first dose will be Day 1.) Relative day will be calculated as date of first dose of LCM minus the current date for days prior to the first dose of LCM (the day prior to first dose will be Day -1). For days after the last dose of LCM, relative day will be calculated as the current date minus the date of last dose of LCM including a "+" to denote posttreatment days (e.g., the day after the last dose will be Day +1). Relative day will not be calculated for partial dates or completely missing dates.

5.1.2.1.3 Study periods

This study consists of a Treatment Period and an End of Study Period.

Treatment Period

This is defined as the period of time from the date of first dose of LCM (Visit 1) to the Termination Visit for participants who complete the study or to the ETV for those who discontinued.

End of Study Period (Taper Period + Safety Follow-up Period)

This is defined as the period of time from the day after the end date of the Treatment Period and extending through to the Final Visit or last contact with the subject. No scheduled visits are planned in the Taper Period. Final Visit is the only scheduled visit in Safety Follow-up Period.

The maximum total duration of the study will be approximately 213 weeks, including an approximate 205-week Treatment Period and up to an 8 week Post-Treatment Period (4-week Taper Period and a Final Visit 30 days after the last dose). The end of the study is defined as the date of the last visit of the last study participant in the study.

5.1.2.1.4 End date of the Treatment Period

The end date of the Treatment Period will be either the date of Termination Visit for participants completing the Treatment Period, or the date of the Early Termination Visit (ETV) for participants who discontinued during the Treatment Period.

5.1.2.1.5 Mapping of assessments performed at Early Termination Visit

Safety assessments at an ETV that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the ETV if the assessment was scheduled to occur at that visit. If the ETV doesn't correspond to a scheduled visit, the assessment will be summarized at the next scheduled visit.

5.1.2.1.6 Definition of Baseline values

Baseline is defined as the last non-missing value collected prior to the first dose of LCM in the first LCM study. The Baseline values in EP0034 and SP0848 will be used as Baseline for safety variables in EP0151, if not stated otherwise. Visit 13/Termination Visit of EP0034 or SP848 will be Visit 1, Week 0 for EP0151. The vital signs measured after the 3 minute measurement in supine position of EP0034 at Visit 13/Termination Visit will be used as vital signs at Visit 1, Week 0 for EP0151.

5.1.2.1.7 Study visit labeling

Visits will be labelled in table summaries (according to the schedule outlined in Section 1.3 of the protocol) as follows:

- "Baseline"
- "Visit X, Week X" for scheduled visits during the Treatment Period
- "Termination Visit"
- "Last Visit", which is the last non-missing assessment during the Treatment Period. All

scheduled and unscheduled assessments within this time period will be considered during the Treatment Period

- "Final Visit"

Listings will also include "Unscheduled Visit" and "Early Termination Visit" as applicable.

5.1.2.2 Body mass index (BMI)

BMI will be calculated using the formula:

BMI = weight (kg) / (height [m])^2

5.1.2.3 Exposure duration

The overall duration of LCM exposure for each participant will be calculated as the date of the last dose of LCM minus the date of the first dose of LCM plus 1 day. Gaps in treatment or days with unknown dosing will not be subtracted from the duration of exposure. The duration of LCM exposure will be summarized descriptively, separately, as a continuous parameter (in days) and as a categorical parameter, where categories will be defined using the following cumulative 6-month intervals for the Treatment Period: >0 months, >6 months, >12 months, >18 months, >24 months, >30 months, >36 months, >42 months, and >48 months, where 1 month is defined as 28 days.

Participant-years of LCM exposure in the study is calculated as the duration of exposure (days) divided by 365.25.

Participant-years of LCM exposure will be summarized using the following cumulative 6-month time intervals for the Treatment Period: >0 months, >6 months, >12 months, >18 months, >24 months, >30 months, >36 months, >42 months, and >48 months.

Participant-months of exposure will be calculated as the sum of days of exposure divided by 28.

5.1.2.4 Modal and maximum daily LCM dose

The modal daily LCM dose (mg/kg/day) is defined as the daily LCM dose the participant received for the longest duration during the Treatment Period in EP0151.

The maximum daily LCM dose (mg/kg/day) is defined as the highest total daily dose a participant received during the Treatment Period in EP0151.

Maximum daily LCM dose will be summarized as a continuous parameter (in mg/kg/day). Modal daily LCM dose will be summarized as a continuous (in mg/kg/day) and categorical parameter, using the following categories (mg/kg/day) for the Treatment Period: 0.0 to <4.0, ≥4.0 to <6.0, ≥6.0 to <8.0, ≥8.0 to <10.0, ≥10.0 to <12.0, and ≥12.0.

The modal and maximum daily dose calculations are based on the number of days a participant was on a given daily dose. Gaps in LCM dosing will be excluded from the determination of modal and maximum daily dose (i.e., no imputation for days with missing dosing log information will be performed). If a participant was on two different LCM doses for the same duration of time (i.e., a tie when calculating modal daily dose), the modal daily dose will be set to the lower of the doses.

In summary tables and listings, modal daily dose will be presented with the following column headers: <4mg/kg/day to represent doses from 0 to <4.0mg/kg/day, 4mg/kg/day to represent

doses 4.0 to <6.0mg/kg/day, 6mg/kg/day to represent doses 6.0 to <8.0mg/kg/day, 8mg/kg/day to represent doses 8.0 to <10.0mg/kg/day, 10mg/kg/day to represent doses 10.0 to <12.0mg/kg/day, and ≥12 mg/kg/day to represent doses greater than or equal to 12.0mg/kg/day.

5.1.2.5 Completer cohorts

A completer cohort will be defined as the subset of participants in the SS that were enrolled and treated with LCM for a specified duration of time. For example, a 12-month completer cohort consists of participants enrolled and treated with LCM for at least 12 months where a month is defined as 28 days.

Participants will be classified as belonging to one of the following completer cohorts for the purpose of subgroup analyses:

- 12 months
- 24 months
- 36 months
- 48 months

5.1.2.6 Protocol Deviations

Important protocol deviations are deviations from the protocol that could potentially have a meaningful impact on study conduct or on the key safety outcomes for an individual study participant. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the appropriate protocol-specific document. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations.

In general, protocol deviations will be considered according to the following general categories:

- Inclusion criteria
- Exclusion criteria
- Withdrawal criteria
- Prohibited concomitant medications
- LCM dosing regimen
- Procedural non-compliance

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock. A list of participants with important protocol deviations will be agreed upon during the Data Evaluation Meetings (DEMs) and will be documented in the DEM minutes.

5.1.2.7 Treatment assignment and treatment groups

This is an open-label study; participants will not be randomized.

Where specified within this SAP, data will either be summarized by age group overall across all LCM doses or by modal daily dose (Section 5.1.2.4).

5.1.2.8 Center pooling strategy

No pooling of centers is planned for this study.

5.1.2.9 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® v16.1). Medications will be coded using the World Health Organization Drug Dictionary (WHODD SEP/2013). Medical procedures will not be coded.

5.1.2.10 Hospital stay duration

The duration of each hospital stay will be calculated as the discharge date minus the admission date (Hospitalization/Emergency Room [ER] Visit Date on the eCRF module) plus 1 day for hospital stays with a discharge date.

5.2 Participant Disposition

The number of participants screened, and number and percentage of participants who were screen failures, broken down by primary reason for screen failure, will be presented for all screened participants.

The date of first participant in (date of earliest Visit 1 for this study), date of last participant out (date of final scheduled or unscheduled visit), number of screened participants, and the number of participants in SS, will be summarized overall and by investigator site. Participants who transfer sites will be summarized according to their original site.

A summary of disposition of analysis sets will be provided for all screened participants. The following will be summarized:

- The number and percentage of participants in the SS

Additionally, a summary of disposition and discontinuation reasons will present the following for all participants in the SS:

- The number and percentage of participants starting the study
- The number and percentage of participants completing the study
- The number and percentage of participants completing <12 months, ≥12 to <24 months, ≥24 to <36 months, ≥36 to <48 months, and ≥48 months where 1 month is defined as 28 days
- The overall number and percentage of participants discontinuing and the number and percentage of participants discontinuing by primary reason for discontinuation.

A summary of discontinuations due to AEs for SS will present the number and percentage of participants who discontinued from this study due to AEs broken down by type of AE.

The number and percentages of participants impacted by COVID-19 will be presented for each visit, overall and by impact category, for each relationship to COVID-19 as well as any relationship, overall and by country, for all participants in the SS. This will also be presented in the participant data listings. Relationship categories include confirmed COVID-19, suspected COVID-19, general circumstances around COVID-19 without infection, and Other. The table of

impact of COVID-19 for any reason includes only the events within the first three relationship categories.

5.3 Primary Endpoint(s) Analysis

In this open-label extension study, no statistical modelling will be used for analysis of the primary endpoints. The primary endpoints will be presented in descriptive statistics in the respective sections.

5.3.1 Definition of endpoints

TEAEs reported by the study participant or caregiver or observed by the Investigator

TEAEs will be defined as those events which started on or after the date of first dose of LCM in EP0151, or events for which severity worsened on or after the date of first dose of LCM in EP0151. AEs which occur within 30 days after final dose of LCM in EP0151 will be considered treatment-emergent.

Withdrawals from study due to TEAEs

Primary reason for premature study termination is collected in eCRF, one of which is AE. Together with the AE information for such participants collected in eCRF, early termination due to TEAE will be derived based on the definition of TEAE.

Withdrawals from study due to SAEs

The premature study termination due to AE collected in eCRF will be further considered for AEs indicated as serious in the eCRF.

Modal daily dose (mg/kg/day)

Definition of modal daily dose is in Section 5.1.2.4.

Maximum daily dose (mg/kg/day)

Definition of maximum daily dose is in Section 5.1.2.4.

5.4 Secondary Endpoint(s) Analysis

Not applicable.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

5.6 (Other) Safety Analyses

All safety variables will be analyzed by descriptive methods for the SS.

5.6.1 Extent of Exposure

The duration of LCM exposure (days), as defined in Section 5.1.2.3, will be summarized as a continuous parameter (in days). In addition, the duration of LCM exposure will be summarized using the cumulative 6-month time intervals for the Treatment Period, as defined in Section 5.1.2.3.

Participant-years of LCM exposure will be summarized using the cumulative 6-month time intervals for the Treatment Period, as defined in Section 5.1.2.3.

The maximum daily LCM dose (mg/kg/day), as defined in Section 5.1.2.4, will be summarized descriptively.

The modal daily LCM dose (mg/kg/day), as defined in Section 5.1.2.4, will be summarized descriptively. In addition, the number of participants and participant-years exposed in each of the modal daily LCM dose categories (mg/kg/day) will be summarized for the Treatment Period, as defined in Section 5.1.2.4.

Most recent study medication for PDILI will be listed for subjects in cases when PDILI occurred.

5.6.2 Adverse Events

AEs will be tabulated by MedDRA system organ class (SOC) and MedDRA preferred term (PT). The number and percentage of participants experiencing each event at least once will be summarized. All summaries will be sorted alphabetically by SOC and by frequency of events within PTs, starting with the most frequent event overall.

AEs will be classified as ongoing at entry, treatment-emergent and post-treatment. Ongoing AEs at entry are defined as AEs which had an onset date prior to the first EP0151 dose of LCM. TEAEs will be defined as those events which started on or after the date of first dose of LCM in EP0151, or events for which severity worsened on or after the date of first dose of LCM in EP0151. AEs which occur within 30 days after final dose of LCM in EP0151 will be considered treatment-emergent. Post-treatment AEs are defined as AEs which had an onset date after 30 days after the last dose of LCM.

All AEs reported during the study including ongoing AE at entry and post-treatment AEs will be provided in a participant data listing. Ongoing AEs from EP0034 and SP848 will be followed up and reported in this study.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of participants with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE. The number and percentage of participant discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of participants with TEAEs leading to death (if applicable) will also be summarized.

The number and percentage of participants who discontinued due to SAE (regardless of treatment emergent) will also be summarized.

The following summaries of AEs will be provided by MedDRA primary SOC and PT:

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of ongoing AEs at EP0151 study entry
- Incidence of TEAEs leading to discontinuation
- Incidence of SAEs leading to discontinuation
- Incidence of TEAEs related to potential drug-induced liver injury (PDILI) (defined in

Appendix 6.1.7)

- Incidence of TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of non-serious TEAEs occurring in at least 5% of participants
- Incidence of TEAEs by maximum intensity
- Incidence of other significant TEAEs (defined in Appendix 6.1.6)
- Incidence of drug-related TEAEs by seriousness
- Incidence of TEAEs by 100 participant-months of exposure. The event rates are derived using the total number of TEAEs, including unique and non-unique TEAEs, divided by the participant-months exposed, and multiplied by 100.

In addition, summaries for the incidence of TEAEs overall, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation, incidence of SAEs leading to discontinuation, TEAEs related to PDILI, other significant TEAEs, and pediatric growth-, neurodevelopment-, behavior-, and endocrine-related TEAEs will be repeated presenting the site and participant number of all those participants experiencing each TEAE as well as in participant data listings. Pediatric growth-, neurodevelopment-, behavior-, and endocrine-related TEAEs will determined by manual medical review of reported MedDRA PTs.

5.6.3 Additional Safety Assessments

5.6.3.1 Clinical laboratory evaluations

Starting from Visit 2, blood specimens for routine assay of hematology and clinical chemistry testing will be analyzed by the local laboratory affiliated with the site. The individual laboratory parameter result data will not be collected in the eCRF; however, the Investigator will report any out of range results judged to be clinically significant as an AE.

No laboratory data will be summarized in tables. Laboratory test for PDILI will be listed if it occurred. Blood sample collection for pharmacokinetics for PDILI and suspected hepatic event for PDILI will be listed if it occurred.

5.6.3.2 Vital Signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate) will be assessed in a semi-supine position after 5 minutes rest throughout the study, according to the tabular schedules of procedures in Section 1.3 of protocol. Body weight and height will also be assessed throughout the study, according to the tabular schedules of procedures. BMI will be derived as defined in Section 5.1.2.2.

5.6.3.2.1 Vital Sign Values Over Time

All summaries of vital signs, body weight, height, and BMI will only summarize variables planned based on the protocol. However, both planned and unplanned variables will be provided in participant data listings.

Observed values of SBP, DBP, pulse rate, body weight, height and BMI will be summarized for each scheduled visit. Change from Baseline for SBP, DBP, pulse rate, body weight, height, and BMI will be summarized for all scheduled post-baseline visits.

5.6.3.2.2 Individual Participant Changes of Vital Sign Values

Markedly abnormal (MA) values are defined as those MA values at scheduled or unscheduled visits which occur on or after the first EP0151 LCM administration through to the end of the study. While referring to the MA criteria, age at time of assessment should be considered by adding time between informed consent and the visit date.

The number and percentage of participants with a MA value, MA low value, and MA high value, at each post-Baseline visit and Final Visit, for which SBP, DBP, pulse rate, and body weight are scheduled to be assessed, will be presented. Percentages will be relative to the number of participants with a value at each time point.

The abnormal vital sign criteria are defined as follows:

Table 5–1: Vital signs abnormality criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	6m - <3y	<90 >150
	3y - <12y	<60 >130
SBP (mmHg)	6m - <3y	<70 >120
	3y - <12y	<80 >140
DBP (mmHg)	6m - <3y	<45 >75
	3y - <12y	<50 >80
Body Weight	1m - <17y	<3% or >97% of the normal body weight growth curve ranges[a] based on gender and the age of participant on date of weight assessment

Abbreviations: m=months, y=years. A month is defined as 28 days; a year is defined as 365.25 days.
[a] Source: http://www.cdc.gov/growthcharts/.

A participant data listing of all vital signs for participants with an AE mapped to the PT bradycardia will be presented.

A participant data listing of all vital signs values including body weight, height, and BMI for all participants will be presented. A separate listing including MA vital signs values will also be presented. Vital signs for PDILI will be listed if it occurred.

5.6.3.3 Other safety endpoint(s)

Where appropriate, suicidality will be assessed by trained study personnel using the Columbia-Suicide Severity Rating Scale (C-SSRS; Columbia University Medical Center, 2008).

The "Already Enrolled" version of the C-SSRS should be completed at the Termination Visit or Early Termination Visit if the participant reaches 6 years of age by the time that visit is conducted. Participants who are ≥6 years of age who require additional treatment with LCM oral solution and are approved to continue will be administered the "Already Enrolled" version of the C-SSRS at the first visit (scheduled or unscheduled) which occurs upon reaching 6 years of age. The "Already Enrolled" C-SSRS version will continue to be administered at each subsequent visit (scheduled or unscheduled) up to and including the Termination or Early Termination Visit.

Participant data listings of the data for the C-SSRS will be provided. No summaries of these results are planned.

5.7 Other Analyses

Not applicable.

5.8 Subgroup analyses

No other subgroup analyses are planned.

5.9 Interim Analyses

Not applicable.

5.10 Data Monitoring Committee (DMC) or Other Review Board

Not applicable.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1 Non-key analysis specifications

6.1.1 Baseline characteristics and demographics

Demographics and baseline characteristics will be summarized descriptively for the SS. The summary comprises age (years) at entry into EP0151, age (years) at entry into first pediatric study, and age at entry into EP0151 categorized as (24 months - <12 years), racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other/Mixed), ethnicity (Hispanic or Latino, and not Hispanic or Latino), weight (kg), height (cm) and BMI (kg/m^2). The number of participants and percentage for age groups, gender and countries will also be presented for the SS.

Demographic data will also be listed for the SS.

6.1.2 Protocol deviations

Important protocol deviations defined in the important protocol deviations document, and additionally identified at the DEMs, will be listed. In addition, the number and percentage of

participants with at least 1 important protocol deviation will be summarized overall and by category of important protocol deviation (as defined in Section 5.1.2.6) for the SS.

6.1.3 Medical history

The number and percentage of participants with a medical history condition (except epilepsy), including both resolved and ongoing conditions that were not reported in the parent studies, will be summarized overall and by MedDRA® primary SOC and PT for the SS.

Lifestyle and family medical history for PDILI participants will be listed if it occurred.

6.1.4 Concomitant diseases and conditions

The number and percentage of participants with concomitant diseases and conditions (medical history conditions noted as ongoing at study entry for the EP0151 study), except epilepsy, will be summarized by SOC and PT for the SS.

6.1.5 Concomitant medications

Concomitant AEDs taken at the start of the EP0151 Treatment Period are defined as AEDs taken concomitantly with LCM at the time of first dose of LCM in EP0151. Ongoing concomitant medications from EP0034 and SP848 will be followed up and reported in this study.

The number of concomitant AEDs taken at the start of the EP0151 Treatment Period will be summarized for the SS based on the following categorization: 0 AEDs, 1 AEDs, 2 AEDs, 3 AEDs, and >3 AEDs. The number and percentage of participants taking concomitant AEDs at the start of the EP0151 Treatment Period will be summarized, separately, by WHODD chemical subgroup (level 4) and medication name, for the SS. AEDs taken as rescue medication will be excluded from the summary.

Concomitant AEDs taken during the EP0151 Treatment Period are defined as AEDs taken concomitantly for at least one day in common with LCM in EP0151.

The number and percentage of participants taking concomitant AEDs during the EP0151 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and medication name, for the SS. AEDs taken as rescue medication will be excluded from the summary.

VNS is allowed and will not be counted as a concomitant AED.

The number and percentage of participants taking concomitant non-AEDs during the EP0151 Treatment Period will be summarized overall and, separately, by WHODD anatomical main group (level 1) and therapeutic subgroup (level 2), for the SS.

Potential hepato-toxic medications inquiries and physical examination for PDILI will be listed if it occurred.

6.1.6 Other significant AEs

Table 6–1: Other significant AEs

MedDRA Preferred Term
CARDIAC AND ECG RELATED TERMS
Atrioventricular block third degree

MedDRA Preferred Term
Atrioventricular block second degree
Bradyarrhythmia
Bradycardia
Cardiac pacemaker insertion
Atrial fibrillation
Atrial flutter
Sinus bradycardia
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased
Sick sinus syndrome
Atrial conduction time prolongation
Atrioventricular dissociation
Conduction disorder
Cardiac arrest
Cardiac fibrillation
Cardiac flutter
Sinus arrest
Torsade de pointes
Ventricular asystole
Ventricular flutter
Ventricular tachyarrhythmia
Implantable defibrillator insertion
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation
Suicide attempt
Intentional self-injury

MedDRA Preferred Term
Self injurious behaviour
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder
Decreased appetite
Diet refusal
Hypophagia
Food aversion
Abnormal behaviour

6.1.7 AEs for PDILI

The following MedDRA PTs are defined as AEs for PDILI:

Table 6–2: AEs for PDILI

MedDRA Preferred Term for PDILI
Acute hepatic failure
Alanine aminotransferase increased
Allergic hepatitis
Aspartate aminotransferase increased
Asterixis
Blood bilirubin abnormal
Blood bilirubin increased
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Chronic hepatitis

MedDRA Preferred Term for PDILI
Coma hepatic
Cryptogenic cirrhosis
Drug-induced liver injury
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic failure
Hepatic infiltration eosinophilic
Hepatic necrosis
Hepatic steatosis
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatotoxicity
Hyperbilirubinaemia
Icterus index increased
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Liver disorder
Liver injury
Mixed liver injury
Non-alcoholic steatohepatitis
Ocular icterus
Subacute hepatic failure

6.1.8 Health care resource use

For health care resource use parameters, the following will be evaluated: concomitant medications (see Section 6.1.5), medical procedures, health care provider consultations not foreseen by the protocol, and hospitalization/ER visits.

6.1.8.1 Medical procedures

The number of concomitant medical procedures per participant will be summarized for the Treatment Period. The number of concomitant medical procedures per participant will be summarized using the categories 0, 1, 2, and 3 or more.

Participants who had any concomitant medical procedures during the course of the study based on the Concomitant Medical Procedures eCRF module will be listed.

6.1.8.2 Healthcare provider consultations

The number of healthcare provider consultations per participant for the Treatment Period will be summarized. The number of healthcare provider consultations will be summarized using the categories 0, 1, 2, 3, 4, and 5 or more.

All healthcare provider consultations data will be listed.

6.1.8.3 Hospital stays and ER visits

The number of hospital stays per participant during the Treatment Period will be summarized. The number of hospital stays will be summarized using the categories 0, 1, 2, 3, 4, and 5 or more. The number and percentage of participants with specific reasons for duration of hospital stays will be summarized for the duration of the Treatment Period.

The durations of hospital stays for the Treatment Period will be summarized. Duration of hospital stays (as defined in Section 5.1.2.10) will be categorized as 0 days, 1-5 days, 6-10 days, 11-15 days, and >15 days, and summarized for the duration of the Treatment Period.

An event logged on the Hospitalization/ER Visit eCRF module where ER is marked as initial entry point will be defined as an ER visit. An ER visit with a participant transfer to an inpatient general ward will also be counted as a hospitalization. However, all other instances of ER visits (where participant transfer is not to an inpatient general ward) will not be counted as hospitalizations. Descriptive statistics for the number of ER stays during the Treatment Period will be presented. The number of ER visits will be summarized using the categories 0, 1, 2, and 3 or more. The number and percentage of participants with specific reasons for duration of ER visits will be summarized for the duration of the Treatment Period.

Hospitalizations with either a partial admission or discharge date are ignored for the calculation of duration of hospital stay. However, such hospitalizations are counted for the number of hospital stays. Participants with no hospital stays will have a duration of 0 days. Should distinct records for hospital stays overlap, then the days during the overlap will only be counted once. Similarly this also applies for ER visits.

All hospitalization and ER data will be listed.

6.2 Appendix 3: Changes to Protocol-Planned Analyses

No changes to protocol planned analyses.

7 REFERENCES

This section is not applicable for this study.

Approval Signatures

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Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 09-Dec-2020 19:36:48 GMT+0000
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