# STATISTICAL ANALYSIS PLAN

## Study: SP848

## Product: Lacosamide

**AN OPEN-LABEL STUDY TO DETERMINE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM ORAL LACOSAMIDE (LCM) AS ADJUNCTIVE THERAPY IN CHILDREN WITH EPILEPSY**

| SAP/Amendment Number | Date |
|---|---|
| Final SAP | 27 Apr 2015 |
| SAP – Amendment 1 | 18 Dec 2015 |
| SAP – Amendment 2 | 8 Mar 2019 |
| SAP – Amendment 3 | 25 Nov 2019 |
| SAP – Amendment 4 | 15 Jan 2021 |

# TABLE OF CONTENTS

# List of Tables

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AED | antiepileptic drug |
| BCR | borderline or clinical range |
| BMI | body mass index |
| BRIEF® | Behavior Rating Inventory of Executive Function® |
| BRIEF®-P | Behavior Rating Inventory of Executive Function® - Preschool Version |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CBCL | Child Behavior Checklist |
| COVID-19 | coronavirus disease 2019 |
| CRF | Case Report Form |
| CV | coefficient of variance |
| DBP | diastolic blood pressure |
| DRM | Data Review Meeting |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| ER | emergency room |
| ETV | Early Termination Visit |
| FAS | Full Analysis Set |
| HRQoL | health-related quality of life |
| IIL | Initiating intravenous lacosamide Group |
| ILAE | International League Against Epilepsy |
| LCM | Lacosamide |
| MA | markedly abnormal |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| OLL | Open-label lacosamide Group |
| PDILI | Potential Drug Induced Liver Injury |
| PedsQL | Pediatric Quality of Life Inventory |
| PK | pharmacokinetic |
| PK-PPS | Pharmacokinetic Per-Protocol Set |
| PT | preferred term |
| RxL | Prescription lacosamide (eg, VIMPAT) Group |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SOC | system organ class |
| SPD | Specification of Protocol Deviations |
| SS | Safety Set |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| ULN | upper limit of normal |
| VNS | vagus nerve stimulation |
| 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 SP848.

# 2 PROTOCOL SUMMARY

## 2.1 Study objectives

The objectives of this study are:

- To obtain information about the safety, tolerability, and pharmacokinetic (PK) of Lacosamide (LCM) during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long-term exposure
- To allow study participants who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow study participants who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM

## 2.2 Study variables

## 2.3 Safety variables

### 2.3.1 Primary safety variables

The primary safety variables are as follows:

- Incidence of Treatment Emergent Adverse events (TEAEs)
- Incidence of Serious Adverse Events (SAEs)
- Subject withdrawal from the study due to TEAEs

### 2.3.2 Other safety variables

The other safety variables are:

- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner Stage (if applicable)
- Achenbach Child Behavior Checklist (CBCL) for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior

- Bayley-III scales for children <18 months of age at time of enrollment (applicable only to study participants enrolled in English-speaking countries)
- Cognitive function assessments (Behavior Rating Inventory of Executive Function – Preschool Version [BRIEF-P]/ Behavior Rating Inventory of Executive Function [BRIEF]) (if applicable) for children >=2 years of age

  LCM palatability and ease of use questionnaire.

### 2.3.3 Pharmacokinetic variables

#### 2.3.3.1 Primary Pharmacokinetic variables

No primary PK variables are defined for this study.

#### 2.3.3.2 Other Pharmacokinetic variables

The other PK variables are:

- Plasma concentration of LCM (for population PK analysis) and concomitant antiepileptic drugs (AEDs)

### 2.3.4 Efficacy variables

#### 2.3.4.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

#### 2.3.4.2 Secondary efficacy variables

The secondary efficacy variables, based on daily seizure diaries are:

- Percent change from Baseline in 28-day partial-onset seizure frequency
- ≥50% reduction in 28-day partial-onset seizure frequency
- ≥75% reduction in 28-day partial-onset seizure frequency
- Seizure days per 28 days (subjects with generalized seizures only)
- Seizure-free status

#### 2.3.4.3 Other efficacy variables

The other efficacy variables are:

- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)
- All seizure frequency analyses as described in secondary efficacy variables (presented for the overall Treatment Period only) may be additionally presented by modal daily dose group, by seizure type, by seizure classification subgroup, by time interval, by visit or time period, or by completer cohort.

## 2.4 Study design and conduct

### 2.4.1 Study description

#### 2.4.1.1 Study participants enrolling from SP847 or other LCM pediatric clinical studies in epilepsy (rollover study participants)

Study participants who complete SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or study participants from another applicable LCM pediatric clinical study in epilepsy and who choose to enter the open-label study (rollover study participants), will begin on the LCM dose that they were receiving at the end of the previous pediatric study. Study participants will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected study participants, concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy. New concomitant AEDs may be introduced as treatment if the medication has been approved by the Regulatory Authorities in the country in which the subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When study participants are withdrawn from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for study participants who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

#### 2.4.1.2 Study participants enrolling directly into SP848

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously received LCM will be permitted to enroll directly into SP848.

Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll at approximately 9 sites in Japan. Beginning with Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will directly enroll into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control. Subjects will be able to

receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator.

SP848 includes subjects ≥1 month to ≤18 years of age since subjects who complete SP847 or another applicable LCM pediatric epilepsy study in subjects <18 years of age may have aged to 18 years old by the time they complete that study and enroll in SP848.

The same study conditions described in Section 2.4.1.1 (e.g., minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

### 2.4.2 Tabular schedule of study procedures

The schedule of the study procedures for SP848 are provided in Section 16.1 of the study protocol and country specific protocol amendments for Japan and China.

## 2.5 Determination of sample size

Approximately 42 study participants from the SP847 study will be eligible to enroll in this open-label study. Other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for study participants ≥4 years of age.

Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848. Protocol Amendment 8 allows an enrollment increase from 75 to 100 eligible pediatric subjects ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of subjects down to 1 month of age.

In total, up to approximately 400 subjects may be eligible to participate in SP848.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.1 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 study participants in each category will be

presented. The denominator for percentages will be based on the number of study 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 study 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
- Coefficient of variance (CV[%]) will be presented with 1 decimal place
- 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 study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥1 month to <4 years
- ≥4 to <18 years
- Total ≥1 month to <18 years
- ≥18 years
- All subjects

Summaries for PedsQL will be presented overall for all applicable study participants and additionally based on the subject's age at Baseline (using the Baseline definition in Section 3.3), using the following age groups:

- ≥1 month to ≤12 months
- >12 months to ≤24 months
- >2 years to ≤4 years
- ≥5 to ≤7 years
- ≥8 to ≤12 years
- ≥13 to ≤18 years
- Total ≥5 years to ≤18 years

Summaries for CBCL/1½-5 will be presented overall for all applicable study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥18 months to <2 years
- ≥2 to <4 years
- Total <4 years

- ≥4 to <6 years

Summaries for CBCL 6-18 will be presented overall for all applicable study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥6 to <12 years
- ≥12 to <16 years
- Total ≥6 to <16 years
- ≥16 years

Summaries for BRIEF-P will be presented overall for all applicable study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥2 to <4 years
- ≥4 to <5 years

Summaries for BRIEF will be presented overall for all applicable study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥5 to <12 years
- ≥12 to <16 years
- Total ≥5 to <16 years
- ≥16 years

Summaries for Bayley-III assessments will be presented overall for all applicable study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥1 to <6 months
- ≥6 months to <1 year
- ≥1 year to <18 months

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

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, subject number and visit (where applicable).

## 3.2 General study level definitions

### 3.2.1 Analysis time points

#### 3.2.1.1 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 SP848 (ie, not the first dose of LCM from the previous study in which study

participants participated prior to SP848 for long-term follow-up study participants). Unless otherwise noted, all references to the last dose of LCM in this SAP refer to the last dose of LCM in the study.

#### 3.2.1.2 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). For days prior to the first dose of LCM (the day prior to first dose will be Day -1), relative day will be calculated as the current date minus the date of first dose of LCM. 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 post-treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial or missing dates.

### 3.2.2 Study periods

This study consists of a Treatment Period and a Post-Treatment Period.

Treatment Period

This is defined as the period of time from the date of first dose of LCM in SP848 to the latter of the last LCM dose date and the study Termination Visit (ie, Early Termination Visit) date.

The Treatment Period is further broken down into the Titration Period and the Post-Titration Period for direct enrollers:

- Titration Period: defined as the date of the first dose of study medication to the day prior to date of Visit 1 or the date of Early Termination (ET) visit in the situation where a subject discontinues prior to the last visit in the Titration Period.
- Post-Titration Period: defined as the date of Visit 1 to the end of the Treatment Period.

Post-Treatment 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 Clinic Visit or last contact with the subject.

### 3.2.3 Mapping of assessments performed at Early Termination Visit

Safety and efficacy assessments at an Early Termination Visit (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. Such assessments will also be considered for Last Visit. Study participants who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. For those study participants the ETV will be mapped to the next scheduled visit, ie, the assessments documented at Visit 13/ETV will be assigned to the next scheduled visit, for which the corresponding assessment is scheduled, following the last documented visit.

In particular, assessments which are done at all visits during the Treatment Period (eg, vital signs, body weight and height), will have ETVs corresponding to a scheduled visit mapped to the corresponding scheduled visit.

For study participants enrolled from sites in Japan, they are allowed to stay in the study longer than 2 years. Such study participants will have a separate ETV if they are in the study after Visit 13.

### 3.2.4 Study visit labeling

Visits will be labeled in table summaries (according to the schedule outlined in Section 16.1 of the protocol) as follows:

- "Screening Visit" for study participants who directly enrolled into SP848
- "Titration Visit X" for scheduled visits during titration for study participants who directly enrolled into SP848
- "Visit X, Week X" for other scheduled visits during the Treatment Period
- "Last Visit" (see below in Section 3.2.6 for further information)

Listings will also include "Unscheduled Visit" as applicable.

### 3.2.5 Monthly time intervals

A month is defined as 28 days and time intervals based on monthly durations are defined as multiples of 28 days (eg, 12 months is defined as 336 days). A subject is included in the analysis for a 3-month interval if they are exposed to LCM at any time during that time interval.

### 3.2.6 Last Visit

The Last Visit for all assessments in SP848 is the last non-missing assessment during the Treatment Period. All scheduled and unscheduled assessments within this time period will be considered. Last Visit will be determined separately for each study procedure where Last Visit is mentioned within this document.

### 3.2.7 Exposure duration

The overall duration of LCM exposure for each subject 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, 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.

Subject-years of LCM exposure in the study is calculated as the duration of exposure (days) divided by 365.25. Subject-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, where 1 month is defined as 28 days.

### 3.2.8 Modal and maximum daily LCM dose

The modal daily LCM dose (mg/kg/day) is defined as the daily LCM dose the subject received for the longest duration during the Treatment Period in SP848.

The maximum daily LCM dose (mg/kg/day) is defined as the highest total daily dose a subject received during the Treatment Period in SP848.

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. This will require that tablet doses in mg/day be converted to mg/kg/day. The following steps will be applied:

1. For days for which a subject received oral solution, the total daily dose in mg/kg/day will be classified into 1 of the above categories on a daily basis.
2. For days for which a subject received tablets, the total daily dose in mg/day will be converted to mg/kg/day by dividing the total daily dose in mg/day by the most recently available body weight; the derived dose in mg/kg/day is then classified into 1 of the above categories on a daily basis.
3. Once all total daily doses are converted to mg/kg/day and classified into 1 of the above categories, the modal daily dose is the dose category which was most frequent.

Should study participants receive both oral solution and an oral tablet on the same day, then the individual tablet dose in mg is converted to mg/kg by dividing by the most recently available body weight, and then the individual dose of oral solution in mg/kg is added to the tablet dose in mg/kg to obtain a total daily dose in mg/kg/day.

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

For efficacy analyses related to seizure frequency, modal daily LCM dose will be presented as the most frequent dose during the interval of observation for seizure frequency parameter.

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.

### 3.2.9 Age and age at first diagnosis

Age at entry into SP848 will be given in years. For direct enrollers and subjects with a complete date of birth available, age at entry into SP848 will use the SDTM derivation in the analysis dataset. For rollover subjects without a complete date of birth available, age at entry into SP848 will be calculated as:

Age at entry into the previous pediatric study + (number of calendar months between the informed consent dates of the previous pediatric study and SP848)/12.

The age at entry into the previous pediatric study is migrated from the previous pediatric study into the SP848 SDTM.

Missing or partial epilepsy diagnosis date will be derived applying all rules for missing data imputation (see Section 4.2.6) and age at diagnosis will use the following formula, where applicable. The age at first diagnosis will be given in years.

If date of birth is a complete date then age at diagnosis will be calculated as:

(Date of first diagnosis of epilepsy – date of birth) / 365.25

If date of birth is a partial date then age at diagnosis will be calculated as:

(Enrollment age in years) – [(Informed consent date – Epilepsy diagnosis date) / 365.25]

If this produces a negative value then age at diagnosis will be set to zero.

### 3.2.10 Weight band

Study participants will be classified as belonging to one of the following weight bands based on their weight at time of enrollment into study SP848:

- <30kg
- ≥30 to <50kg
- ≥50kg

### 3.2.11 Body mass index

Body mass index (BMI) will be calculated using the formula:

$BMI = weight\ (kg) / (height\ (m))^2$

### 3.2.12 Seizure Classification Subgroups

Study participants will be classified as belonging to one of the following seizure classification subgroups based on their seizure classification history for the purpose of disposition, demographic, efficacy, and exposure subgroup analyses:

- POS study participants
  - Study participants from SP0966 who reported only Type I seizures
  - Study participants who reported any Type I seizure
- Generalized seizure study participants
  - Study participants from SP0966 unless they reported only Type I seizures
  - Study participants who reported only Type II seizures
- Unclassified
  - Study participants who reported only Type III seizures

### 3.2.13 Seizure frequency

Seizure frequency per 28 days (SF) will be based on the number of days (D) for which seizure information was provided:

SF = (Number of seizures in the analysis period) x (28/D)

If a seizure cluster is reported, it will be assigned to the correct seizure type and the highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event will be used as the imputed number of seizures for the day on which the cluster occurred. If no other seizures are recorded for that seizure type for the subject in the 28 days prior to the cluster event, the frequency will be set to 1.

If more than 1 cluster event occurred on the same day for a Type II or Type III seizure, the seizure clusters will be assigned to the correct seizure type and the frequency for each cluster event will be set to the highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event. If no other seizures are recorded for that seizure type for the subject in the 28 days prior to the cluster event, the frequency will be set to the number of cluster episodes reported.

If more than 1 cluster event occurred on the same day for a Type I seizure, the seizure clusters will be assigned to the correct seizure type and the overall frequency will be set to the maximum of:

- The highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event
- The number of cluster episodes reported on that day

### 3.2.14 Percent change in seizure frequency

The percent change in seizure frequency per 28 days (PCH) from the Baseline value (B) (using the Baseline definition in Section 3.3) to the Treatment Period interval (T) is defined as:

$$PCH = [(SF_T - SF_B) / SF_B] \times 100$$

where $SF_T$ corresponds to the seizure frequency during the Treatment Period for the relative interval in the open-label study and $SF_B$ corresponds to the Baseline seizure frequency. The frequency for both periods will be standardized to the number of seizures per 28 days.

### 3.2.15 Response to treatment

Response to treatment is based on the percent change in seizure frequency relative to Baseline (using the Baseline definition in Section 3.3). Study participants who experience at least a 50% reduction from Baseline will be considered ≥50% responders. Study participants who experience at least a 75% reduction from Baseline will be considered ≥75% responders.

### 3.2.16 Seizure day

A seizure day is defined as a day where any type of seizure was reported in the seizure diary and seizures were assessed. Days in the seizure diary which are marked as “not done” on the CRF/eCRF will not be counted as a seizure day.

### 3.2.17 Seizure-free day

A seizure-free day is defined as a day where no seizures were reported in the seizure diary and seizures were assessed. Days in the seizure diary which are marked as “not done” on the CRF/eCRF will not be counted as a seizure-free day.

### 3.2.18 Seizure-free status

Study participants will be considered seizure-free for a given period if the subject completes the period, reports zero seizures during the period, and have no more than 10% of days in the period for which seizure data is not available (ie, "not done" is noted on the Seizure Frequency CRF/eCRF module). Seizure diary days where "not done" has been reported for days when study participants were participating in a previous study will not be counted toward the 10% of days with missing seizure diary data (eg, missing seizure data due to a previous study will not count against a subject in the assessment of seizure-free status). If a subject enrolls in the EP0060 iv study, days of participation in EP0060 will also not be considered in the assessment of seizure-free status.

### 3.2.19 Completer cohorts

A completer cohort will be defined as the subset of study participants in the Full Analysis Set (FAS) that were enrolled and treated with LCM for a specified duration of time. For example, a 6-month completer cohort consists of study participants enrolled and treated with LCM for at least 6 months where a month is defined as 28 days.

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

- 6 months
- 12 months
- 18 months
- 24 months
- 30 months
- 36 months
- 42 months
- 48 months

### 3.2.20 Number and percentage of seizure-free days

The number of seizure-free days will be the total number of days within an interval for which daily diary data was available and no seizures were reported. The percentage of seizure-free days will be computed as 100 times the number of seizure-free days in the interval divided by the number of days in the interval for which daily diary data was available. Days without the corresponding daily diary data will not be used in these computations (ie, days where "not done" is marked on the Seizure Frequency CRF/eCRF module). The change in percentage of seizure-free days will be calculated relative to Baseline (using the Baseline definition in Section 3.3).

### 3.2.21 Seizure time intervals

Study participants will be classified as belonging to one of the following time intervals for the purpose of seizure efficacy analyses:

- ≤3 months
- >3 to ≤6 months

- >6 to ≤12 months
- >12 to ≤18 months
- >18 to ≤24 months
- >24 to ≤30 months
- >30 to ≤36 months
- >36 to ≤42 months
- >42 to ≤48 months
- >48 months

### 3.2.22 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≥1 month to ≤18 years of age. The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric study participants ≥1 month to ≤12 months, ≥13 months to ≤24 months, >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. For each subject, the same version that is used at Baseline should be used for 12 months and thereafter the appropriate age versions should be used.

For versions intended for subjects ≤24 months of age, PedsQL infant scale scores will be calculated for each of the following 5 PedsQL scales:

- Physical Functioning
- Physical Symptoms
- Emotional Functioning
- Social Functioning
- Cognitive Functioning

For versions intended for subjects >2 years of age, PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales:

- Physical Functioning
- Emotional Functioning
- Social Functioning
- School Functioning

For versions intended for subjects >8 years of age, Physical Functioning refers to questions "About my health and activities"; Emotional Functioning refers to questions "About my feelings"; Social Functioning refers to questions "How I get along with others"; School Functioning refers to questions "About school".

The PedsQL assessment is retrospective to the prior one month, and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: never, almost never, sometimes, often, or almost always). These scores of 0 to 4 will be transformed by the following formula in order to generate scores of 0, 25, 50, 75, and 100 where a higher value represents a better health-related quality of life (HRQoL):

Item transformed score = 100 – (item raw score x 25)

Each PedsQL scale or dimension score is then calculated as the mean of the transformed item scores from items of the considered dimension. In the case of item-level missing data, these will be replaced by the average of non-missing item scores from the considered dimension, if at least 50% of the items from that dimension are non-missing.

The above algorithm will also be used to calculate the PedsQL total score (all items), the psychosocial health summary score (a combination of the emotional, social and cognitive functioning items), and the physical health summary score (a combination of the physical functioning and physical symptoms items) for each subject ≤24 months of age. Also, the PedsQL total score (all items), the psychosocial health summary score (a combination of the emotional, social and school functioning items) and the physical health summary score (the physical functioning items) will be calculated for each subject >2 years of age. These summary scores will be missing if any of the scale scores contributing to their calculation is missing.

### 3.2.23 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 CRF/eCRF module) plus 1 day for hospital stays with a discharge date.

## 3.3 Definition of Baseline values

In general, Baseline will be defined as the last non-missing value collected prior to the first dose of LCM in the original study for rollover subjects and in SP848 for direct enrollers for safety and efficacy variables unless otherwise noted for a specific type of data. The Baseline value for seizure counts for directly enrolled study participants will be taken from the Historical Seizure Count CRF/eCRF module collected in SP848 in combination with the seizure diary data collected from the date of the Screening Visit to the day prior to the date of first dose of LCM.

For participants enrolling from EP0060 the baselines for the questionnaires will consider each EP0060 enrollment group separately, those are: IIL (Initiating intravenous lacosamide Group: not currently receiving LCM, i.e. LCM naïve), OLL (Open-label lacosamide Group: currently receiving oral LCM in open-label long term study), and RxL (Prescription lacosamide Group: currently receiving prescribed oral LCM from commercial supply, VIMPAT). For ILL group baseline will be Visit 1 from SP848, for OLL group baseline will come from SP848 using above baseline definition, and for RxL group there will be no baseline data as they were on oral LCM prior to EP0060.

## 3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary or secondary outcomes for an individual study participant. The criteria for identifying important protocol deviations and the classification of

important protocol deviations will be defined separately in the Specification of Protocol Deviations (SPD) document. To the extent feasible, rules for identifying protocol deviations will be pre-defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all study participants.

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 Data Review Meeting (DRM) prior to database lock. A list of study participants with important protocol deviations will be agreed upon during the DRM and will be documented in the DRM minutes.

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (COVID-19) will be documented.

## 3.5 Analysis sets

### 3.5.1 Safety Set

The Safety Set (SS) will consist of all enrolled study participants who took at least 1 dose of LCM in this study. All safety analyses will be performed on the SS.

### 3.5.2 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all study participants from the SS having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) on at least 1 visit with documented LCM intake times.

### 3.5.3 Full Analysis Set

The Full Analysis Set (FAS) will be used for the analysis of seizure data and will consist of all study participants in the SS, who have at least 1 completed post-Baseline seizure diary.

## 3.6 Treatment assignment and treatment groups

This is an open-label study; 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 LCM dose (defined in Section 3.2.8).

## 3.7 Center pooling strategy

No pooling of centers is planned for this study.

## 3.8 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 3Q13). Medical procedures will not be coded.

## 3.9 Changes to protocol-defined analyses

### 3.9.1 Handling of dropouts or missing data

The following protocol-defined method of analysis is no longer applicable for this study:

- All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter. Study participants who discontinue from the study prematurely will be evaluated based on the data collected at each visit attended.

This will be replaced with the following method of analysis (see Section 4.2):

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

### 3.9.2 Examination of subgroups

A subgroup for weight which was not protocol-defined has been included in Section 3.2.

# 4 STATISTICAL/ANALYTICAL ISSUES

## 4.1 Adjustments for covariates

No statistical testing is planned; therefore, this section is not applicable for this study.

## 4.2 Handling of dropouts or missing data

### 4.2.1 Missing data

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

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 4.2.2.

### 4.2.2 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 subject 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 maximum of the date of study termination or the date equivalent to 30 days after last intake of LCM.

However, if the study termination 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.

### 4.2.3 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 subject data listings, dates will be displayed as reported.

### 4.2.4 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 subject 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.

However, if a subject 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.

### 4.2.5 Incomplete dates for seizure diary data

Seizure frequency and seizure-free days will be calculated over non-missing diary days during each time interval; days for which seizure diary data were not obtained will not be considered in the calculation of seizure frequency or seizure-free days. As the evaluation of efficacy is not the primary objective of this study, and because this is an uncontrolled study in a variable setting, which allows individualized optimization of dosing of LCM and concomitant AEDs, no summaries assessing the impact of missing seizure diary days are planned.

### 4.2.6 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
- Start and stop dates of seizure diary data

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

### 4.2.7 Missing data due to participation in solution for infusion formulation trials

Study participants who participated in the iv trial EP0060 while also enrolled in SP848 will have missing data for seizure frequency and drug dosing during the period of participation in the iv trial. As the duration of the iv trial is short, approximately 1 to 5 days, no imputation for data missing due to participation in the iv trial will be performed.

Study participants were assigned the same dose in EP0060 as that assigned in SP848 for the two weeks prior to the start of the iv trial. As such, time during the iv trial will not be subtracted from the exposure calculation (ie, exposure will be from the start of LCM treatment in SP848 trial until the date of last dose of LCM in SP848). The duration of treatment during EP0060 is approximately 1 to 5 days.

For the calculation of variables related to seizure frequency, the dates during participation in EP0060 will be considered as not done for the purpose of efficacy analyses for SP848 (ie, the dates will not be considered as days evaluated for seizure frequency). Due to the short nature of

EP0060, only 1 to 5 days of seizure frequency data are expected to be missing due to participation in EP0060.

### 4.3 Interim analyses and data monitoring

No formal interim analysis is planned. However, data may be reported prior to the completion of this study to support annual reports, regulatory submissions, and publications.

### 4.4 Multicenter studies

No multicenter analyses are planned; therefore, this section is not applicable for this study.

### 4.5 Multiple comparisons/multiplicity

No statistical testing is planned; therefore, this section is not applicable for this study.

### 4.6 Use of an efficacy subset of study participants

The FAS, defined in Section 3.5.3, is the primary analysis set for efficacy analyses. No additional efficacy subsets are defined for this study.

### 4.7 Active-control studies intended to show equivalence

This section is not applicable for this study.

### 4.8 Examination of subgroups

Subgroups for this study are defined in the sub-sections of Section 3.2.

## 5 STUDY POPULATION CHARACTERISTICS

### 5.1 Subject disposition

The number of study participants screened (screened study participants include study participants who signed an ICF), in addition to the number and percentage of those study participants who were screen failures, broken down by primary reason for screening failure, will be presented. A summary of disposition of study participants will be provided for all screened study participants. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of study participants screened, number of study participants enrolled, and the number of study participants in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Study participants who transferred sites will be summarized according to their original site.

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

- The number of screened study participants
- The number and percentage of enrolled study participants
- The number and percentage of study participants in the SS
- The number and percentage of study participants in the PK-PPS
- The number and percentage of study participants in the FAS
- The number of study participants from each parent study

- The number of original direct enrollers (excluding Japanese and Chinese direct enrollers)
- The number of Japanese direct enrollers
- The number of Chinese direct enrollers

Additionally, a summary of disposition and discontinuation reasons will present the following for all study participants in the SS (overall and repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively), PK-PPS, and FAS:

The number and percentage of study participants starting the study

The number and percentage of study participants completing <12 months, 12, 24, 36, and ≥48 months of the study.

The number and percentage of study participants completing the study (defined as study participants who have 'Completed subject' selected as status at termination – see Study Termination eCRF module).

The overall number and percentage of study participants discontinuing and the number and percentage of study participants discontinuing by primary reason for discontinuation. If the subject discontinued the study and the Study Termination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of study participants enrolled under each protocol amendment (estimated by date of informed consent) will be presented for all global protocols, and separately, for Chinese direct enrollers from version 5.4 and for Japanese direct enrollers from version 5.3. This will also be presented in the subject data listings.

The number and percentages of subjects 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 subjects in the SS. This will also be presented in the subject data listings.

## 5.2 Protocol deviations

Important protocol deviations defined in the SPD, and additionally identified at the DRM, will be listed. In addition, the number and percentage of study participants with at least 1 important protocol deviation will be summarized overall and by category of important protocol deviation (as defined in Section 3.4) for the SS.

# 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

## 6.1 Demographics and other Baseline characteristics

Demographic variables, unless otherwise specified, will be obtained from the demographics data collected at the time of entry into the previous pediatric LCM study for those study participants who enrolled from SP847 (or other LCM pediatric clinical studies in epilepsy). Demographic variables will be obtained from the Screening Visit for those study participants who directly enrolled into SP848.

Demographic variables will be presented by weight band (using the levels defined in Section 3.2.10), by seizure classification subgroup (using the levels defined in Section 3.2.12) and overall for the SS. The variables to be considered are:

- Age at entry into SP848 (as defined in Section 3.2.9) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years - <18 years) and categorized as (≤18 years and 19 - < 65 years)
- Age at entry into previous pediatric study for study participants from SP847 or other studies and age at entry into SP848 for directly enrolled study participants (years) (as defined in Section 3.2.9)
- Gender
- Weight (kg) at entry into SP848
- Weight band (as defined in Section 3.2.10)
- Height (cm)
- BMI (kg/m$^2$) (as defined in Section 3.2.11)
- 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)
- Vagus nerve stimulation (VNS) use (Active VNS, No VNS, and VNS not active)

A listing of reproductive potential and birth control measures will be provided. No summaries of these results are planned.

## 6.2 Medical history and concomitant diseases

### 6.2.1 Medical history

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

### 6.2.2 Concomitant diseases and conditions

The number and percentage of study participants with concomitant diseases and conditions (medical history conditions noted as ongoing at study entry for the SP848 study), except epilepsy, will be summarized by SOC and PT for the SS.

## 6.3 History of epilepsy

The history of epilepsy uses CRF/eCRF information collected at the time of entry into the previous pediatric LCM study for those study participants who enrolled from SP847 (or other LCM pediatric clinical studies in epilepsy). The history of epilepsy will be obtained from the Screening Visit for those study participants who directly enrolled into SP848.

### 6.3.1 History of seizure types

The number and percentage of study participants experiencing partial-onset seizures (type I), simple partial (type IA), complex partial (type IB), and partial, secondary generalized seizures (type IC), in addition to each seizure category within such, at any time prior to study entry (into the previous study for rollover study participants or into SP848 for those direct enrollers) will be summarized based on the 1981 International League Against Epilepsy (ILAE) Seizure Classification History CRF/eCRF module. This will be summarized for the SS, by seizure classification subgroups.

For POS study participants the following classifications will be used. A subject will be classified as having a history of partial-onset seizures (I) if the subject has a history of simple partial (IA), complex partial (IB), or partial, secondary generalized (IC) seizures. A subject will be classified as having a history of simple partial seizures if the subject has a history of motor signs (IA1), somatosensory or special sensory symptoms (IA2), autonomic symptoms or signs (IA3), or psychic symptoms (IA4). A subject will be classified as having a history of complex partial seizures if the subject has a history of simple partial onset followed by impairment of consciousness with simple partial features (IB1a) or automatism (IB1b), or if the subject has a history of impairment of consciousness at onset with no other features (IB2a) or automatism (IB2b). A subject will be classified as having a history of partial, secondary generalized seizures if the subject has a history of simple partial evolving to generalized (IC1), complex partial evolving to generalized (IC2), or simple partial evolving to complex partial evolving to generalized (IC3) seizures.

For study participants with generalized seizures the following classifications will be used. A subject will be classified as having a history of partial-onset seizures (I) if the subject has a history of simple partial (IA), complex partial (IB), or partial, secondary generalized (IC) seizures. A subject will be classified as having a history of simple partial seizures if the subject has a history of motor signs (IA1), somatosensory or special sensory symptoms (IA2), autonomic symptoms or signs (IA3), or psychic symptoms (IA4). A subject will be classified as having a history of generalized seizures (II) if the subject has a history of absence (IIA), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), or atonic (IIF) seizures. A subject may also be classified as having a history of unclassified epileptic seizures (III).

### 6.3.2 History of seizure characteristics

Quantitative summaries of epilepsy duration and age at diagnosis (as defined in Section 3.2.9) will be summarized for the SS. This will be summarized for the SS, by seizure classification subgroups.

### 6.3.3 Historical seizure counts

The Historical Seizure Counts CRF/eCRF module records the number of seizures per pre-selected ILAE seizure code experienced by the subject during the 4 weeks prior to Baseline.

These data will be provided in a subject data listing. This will be summarized for the SS, by seizure classification subgroups.

## 6.4 Prior and concomitant medications

All prior and concomitant medications will be presented by seizure classification subgroup, age group, weight band and overall. Antiepileptic drugs defined as medications documented on the "Concomitant Medications (AEDs only)" log form. A medical review will be performed to ensure that the medications are documented correctly. A listing of all medications taken during the study will be presented.

### 6.4.1 Number of previous AEDs

The number of previous AEDs defined as AEDs taken and stopped >28 days prior to entry into the study, will be summarized for the SS based on the following categorization: 0 AED, 1-3 AEDs, 4-6 AEDs, and ≥7 AEDs. This summary will be based on the History of Previous AED Treatment CRF/eCRF module for applicable studies which only includes AEDs stopped prior to study entry. For study participants who rolled over from the SP0966 study, previous AEDs are defined as AEDs taken 12 months prior to informed consent date and stopped>28 days prior to entry into SP0966.

### 6.4.2 Concomitant AEDs taken at the start of the SP848 Treatment Period

Concomitant AEDs taken at the start of the SP848 Treatment Period are defined as AEDs taken concomitantly with LCM at the time of first dose of LCM in SP848.

The number of concomitant AEDs taken at the start of the SP848 Treatment Period will be summarized for the SS based on the following categorization: 0 AED, 1 AED, 2 AEDs, 3 AEDs and ≥4 AEDs. The number and percentage of study participants taking concomitant AEDs at the start of the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

### 6.4.3 Concomitant AEDs taken during the SP848 Treatment Period

Concomitant AEDs taken during the SP848 Treatment Period are defined as AEDs taken concomitantly for at least one day in common with LCM in SP848.

The number and percentage of study participants taking concomitant AEDs during the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

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

### 6.4.4 Concomitant medications (excluding AEDs)

The number and percentage of study participants taking concomitant non-AEDs during the SP848 Treatment Period will be summarized overall and, separately, by WHODD anatomical main group (level 1) and therapeutic subgroup (level 2), for the SS.

# 7 MEASUREMENTS OF TREATMENT COMPLIANCE

Information reported on the eCRF regarding LCM dispensed and returned will be reported in subject data listings. No summaries of these results are planned. LCM dosing compliance will be

evaluated through the review of important protocol deviations classified under LCM Dosing Regimen (see Section 3.4).

# 8 SAFETY ANALYSES

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

## 8.1 Extent of exposure

All the summaries described below will also be presented by seizure classification subgroup, using the levels defined in Section 3.2.7, and for the FAS.

The duration of LCM exposure (days), as defined in Section 3.2.7, will be summarized as a continuous parameter (in days) overall, and repeated by weight band using the levels defined in Section 3.2.10. 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 3.2.7.

Subject-years of LCM exposure will be summarized using the cumulative 6-month time intervals for the Treatment Period, as defined in Section 3.2.7.

The maximum daily LCM dose (mg/kg/day), as defined in Section 3.2.8, will be summarized overall, and repeated by weight band using the levels defined in Section 3.2.10.

The modal daily LCM dose (mg/kg/day), as defined in Section 3.2.8, will be summarized, overall, and repeated by weight band using the levels defined in Section 3.2.10. In addition, the number of study participants and subject-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 3.2.8.

Summary statistics (n, mean, SD, minimum and maximum) for the duration of LCM exposure (days) and median daily LCM dose (mg/kg/day) during each of the following analysis periods for direct enrollers: Titration, Post-Titration and Treatment Period will be summarized for the SS. Duration of LCM exposure (days) and median daily LCM dose (mg/kg/day) for the Treatment Period will be summaries for the rollover and all study participants in the SS separately.

## 8.2 Adverse events

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively. Additional tables will also be presented by time interval using the definition in Section 3.2.5. The number and percentage of study 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 30 days after last dose of LCM 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.

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent adverse events and treatment-emergent serious adverse events will be published.

All AEs reported during the study including pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of study participants with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of study participants with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, the overall summary will be presented for the Titration Period, Post-Titration Period and Treatment Period for the direct enrollers and the Treatment Period for the rollover study participants.

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

- Incidence of TEAEs
- Incidence of TEAEs with onset during the Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Post-Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Treatment Period for direct enrollers
- Incidence of TEAEs for direct enrollers
- Incidence of TEAEs for rollover study participants
- Incidence of serious AEs
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of TEAEs leading to discontinuation from the study
- Incidence of TEAEs by relationship to LCM
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs related to Potentially Drug Induced Liver Injury (PDILI) (defined in Appendix 12.3)
- Incidence of pediatric growth-, neurodevelopment-, behavior-, and endocrine-related TEAEs (defined by manual medical review)
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of non-serious TEAEs occurring in at least 5% of study participants by relationship to LCM

- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will also be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively.

- Incidence of TEAEs
- Incidence of serious AEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation from the study
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will be presented for the time intervals (using the definition in Section 3.2.5) of: ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months, >12 to ≤ 15 months, >15 to ≤18 months, >18 to ≤21 months, >21 to ≤24 months, and >24 to ≤ 30 months, >30 to ≤36 months, >36 to ≤42 months, >42 to ≤48 months, >48 months:

- Incidence of all TEAEs with onset during the Treatment Period
- Incidence of all serious AEs with onset during the Treatment Period
- Incidence of all serious TEAEs with onset during the Treatment Period
- Incidence of all TEAEs leading to discontinuation from the study with onset during the Treatment Period
- Incidence of all other significant TEAEs with onset during the Treatment Period (defined in Appendix 12.2)

In addition, summaries for the incidence of TEAEs overall, incidence of serious AEs, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation from study, incidence of other significant TEAEs, TEAEs related to PDILI, and pediatric growth-, neurodevelopment-, behavior-, and endocrine-related TEAEs will be repeated presenting the site and subject number of all those study participants experiencing each TEAE as well as in subject data listings.

## 8.3 Clinical laboratory evaluations

Hematology, blood chemistry (including liver function tests), urinalysis, and endocrinology parameters are assessed throughout the study, according to the tabular schedules of study procedures. Urinalysis will be performed for study participants ≥5 years of age only.

All summaries of laboratory parameters will only summarize parameters planned based on the protocol. However, both planned and unplanned laboratory parameters will be provided in subject data listings. Summaries will include hematology, chemistry and endocrinology results; urinalysis results will be included in subject data listings only.

Observed values of hematology, chemistry, and non-gender specific endocrinology parameters (ie, thyroid stimulating hormone, triiodothyronine [total and serum-free], and thyroxine [total and serum-free]) will be summarized for each visit and Last Visit. Change from Baseline for hematology, chemistry, and non-gender specific endocrinology parameters will be summarized for all post-Baseline visits, and Last Visit. Gender specific endocrinology parameters (ie, follicle stimulating hormone, luteinizing hormone, and testosterone) will be presented similarly, by gender.

A shift table that cross-tabulates Baseline versus maximum result during the Treatment Period in categories of <1 x ULN (upper limit of normal), 1 to <2 x ULN, 2 to <3 x ULN, ≥3 x ULN, and missing will be presented for liver function tests (LFT) which include Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-glutamyl Transferase (GGT), Total Bilirubin, and Alkaline Phosphatase.

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values during the defined Treatment Period at scheduled or unscheduled visits which occur on or after the first SP848 LCM administration through to the end of the study but were normal at Baseline. The age at the time of assessment will be used for determining TEMA. The age at the time of visit/assessment will be obtained using date of informed consent to date of visit.

The number and percentage of study participants with a TEMA value, TEMA low value, and TEMA high value will be summarized, at each post-Baseline visit and Last Visit. Percentages will be relative to the number of study participants with a value at each time point. Criteria for determining if a value is TEMA are detailed in Appendix 12.1.

Serum and urine pregnancy testing will be performed on all females of childbearing potential, according to the tabular schedule of study procedures. Serum and urine pregnancy test results will be listed. No summaries of these results are planned.

PDILI IMP discontinuation criteria as outlined in the protocol, will be evaluated at all laboratory assessments. The number and percentage of study participants meeting PDILI criteria (ie, ALT or AST criteria and/or total bilirubin criteria, and/or presence of symptoms), will be presented by treatment group. Percentages will be based on the number of study participants with a non-missing measurement for the variable of interest at the relevant visit.

## 8.4 Vital signs, physical findings, and other observations related to safety

### 8.4.1 Vital signs, body weight, height, and BMI

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, and temperature), body weight, and height will be collected according to the tabular schedule of study procedures. In addition, BMI will be calculated (as defined in Section 3.2.11) for each visit where weight and height are collected.

Noninvasive blood pressure (systolic and diastolic) and pulse rate will be measured at all visits in a sitting position after at least 3 minutes at rest. Body weight will be determined without shoes and wearing light clothing. Height will be measured without shoes.

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 subject data listings.

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

Markedly abnormal (MA) values are defined as those MA values during the defined Treatment Period at scheduled or unscheduled visits which occur on or after the first SP848 LCM administration through to the end of the study.

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

The abnormal vital sign criteria are defined as follows:

**Table 8–1: Vital signs abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| Pulse Rate (beats/minute) | <6m | <100<br>>180 |
| | 6m - <3y | <90<br>>150 |
| | 3y - <12y | <60<br>>130 |
| | 12y - <17y | ≤50<br>≥120 |
| | ≥17y | ≤50 and a decrease from Baseline of ≥15<br>≥120 and an increase from Baseline of ≥15 |
| Systolic Blood Pressure (mmHg) | <6m | <60<br>>100 |
| | 6m - <3y | <70<br>>120 |
| | 3y - <12y | <80<br>>140 |
| | 12y - <17y | <90<br>>160 |
| | ≥17y | ≤90 and a decrease from Baseline of ≥20<br>≥180 and an increase from Baseline of ≥20 |

**Table 8–1: Vital signs abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| Diastolic Blood Pressure (mmHg) | <6m | <40<br>>65 |
| | 6m - <3y | <45<br>>75 |
| | 3y - <12y | <50<br>>80 |
| | 12y - <17y | ≤50<br>≥105 |
| | ≥17y | ≤50 and a decrease from Baseline of ≥15<br>≥105 and an increase from Baseline of ≥15 |
| Temperature | >1m | >101 °F (38.3 °C) |
| Body Weight | 1m - <17y | <3% or >97% of the normal body weight growth curve ranges[a] based on gender and the age of subject on date of weight assessment |
| | ≥17y | ≥10% change from Baseline (an increase or a decrease) |

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 subject data listing of all vital signs for study participants with an AE mapped to the PT bradycardia or sinus bradycardia will be presented.

A subject data listing of all vital sign values including body weight, height, and BMI for all study participants will be presented. A separate listing including MA vital signs values will also be presented.

### 8.4.2 Electrocardiograms (ECGs)

Standard 12-lead ECGs (2 interpretable recordings [20 to 30 minutes apart]) will be performed throughout the study, according to the tabular schedule of study procedures.

For ECGs, Baseline will be defined as the average of all pre-dose interpretable readings. Assessments with missing time on day of first dose will be assumed pre-dose. For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

Observed values of ECG results will be summarized for each visit and Last Visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits, and Last Visit. This will be summarized overall and repeated by weight band using the levels defined in Section 3.2.10.

The number and percentage of study participants with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, will be summarized for all visits, and Last Visit. Percentages will be relative to the number of study participants with an

ECG assessment at each visit. Study participants are counted at most once at each visit based on the worst observed outcome across all abnormalities reported at that visit.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit will also be provided based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant.

A listing of ECG data will be provided for all study participants with other significant TEAEs in the Cardiac and ECG Related Terms category defined in Appendix 12.2. A subject data listing of all ECG parameter values for all study participants will also be presented. Listings will include results from each recording and the average of all recordings.

The number and percentage of study participants with treatment-emergent ECG abnormalities will be presented for each post-Baseline visit and Last Visit. Abnormalities reported at an unscheduled visit will be summarized under the scheduled visit preceding the unscheduled visit (if the abnormality was not present already at the preceding scheduled visit). Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline. The age at the time of visit/assessment will be used for determining abnormality criteria. The age at the time of assessment will be obtained using date of informed consent to date of visit. All ECG parameter values will be listed for study participants meeting any abnormality criteria.

Abnormality criteria to be used in the determination of ECG abnormalities are defined as follows, where increase and decrease are relative to Baseline values:

**Table 8–2: ECG abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| QT interval (ms) | 1m - <12y | ≥500 |
| | ≥12y | ≥500 or ≥60ms increase from Baseline |
| QTc(F) (ms) | <6m | >490, or >15% increase from Baseline |
| | 6m - <3y | >440, or >15% increase from Baseline |
| | 3y - <12y | >440, or >15% increase from Baseline |
| | ≥12y - <17y | >440, or >15% increase from Baseline |
| | ≥17y | ≥500 or ≥60ms increase from Baseline |
| QTc(B) (ms) | <6m | >490, or >15% increase from Baseline |
| | 6m - <3y | >450, or >15% increase from Baseline |
| | 3y - <12y | >450, or >15% increase from Baseline |
| | ≥12y - <17y | >450, or >15% increase from Baseline |
| | ≥17y | ≥500 or ≥60ms increase from Baseline |
| PR interval (ms) | <6m | >150, or ≥25% increase from Baseline |
| | 6m - <3y | >170, or ≥25% increase from Baseline |
| | 3y - <12y | >180, or ≥25% increase from Baseline |

**Table 8–2: ECG abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| | ≥12y - <17y | >200, or ≥25% increase from Baseline |
| | ≥17y | Treatment-emergent value >200, >220, >250 |
| QRS interval (ms) | <6m | >90, or ≥25% increase from Baseline |
| | 6m - <3y | >90, or ≥25% increase from Baseline |
| | 3y - <12y | >100, or ≥25% increase from Baseline |
| | ≥12y - <17y | ≥110, or ≥25% increase from Baseline |
| | ≥17y | Treatment-emergent value ≥100, >120, >140 |
| Heart rate (bpm) | <6m | <100, >180 |
| | 6m - <3y | <90, >150 |
| | 3y - <12y | <60, >130 |
| | ≥12y | <50, >120 |

Abbreviations: bpm=beats per minute; m=months; ms=milliseconds; QTc=corrected QT interval; y=years. A month is defined as 28 days; a year is defined as 365.25 days.

A subject data listing will be provided that identifies study participants with a clinically significant finding after the first dose of LCM for each type of ECG abnormality.

### 8.4.3 Physical examination

#### 8.4.3.1 Complete physical examination

A complete physical examination will be performed throughout the study, according to the tabular schedule of study procedures.

The complete physical examination will include cardiac and respiratory function via auscultation, temperature measurement, and review of all body systems.

Clinically significant physical examination findings will be reported as AEs.

#### 8.4.3.2 Brief physical examination

A brief physical examination will be performed throughout the study, according to the tabular schedule of study procedures.

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

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

Clinically significant physical examination findings will be reported as AEs.

### 8.4.4 Neurological examination

#### 8.4.4.1 Complete neurological examination

A complete neurological examination will be performed throughout the study, according to the tabular schedule of study procedures.

The complete neurological examination will include selected assessment of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.

Clinically significant neurological findings will be reported as AEs.

Summaries of shift from Baseline to Last Visit will be provided based on categories normal, abnormal, not clinically significant, and abnormal, clinically significant. A listing of neurological examination findings from the complete neurological examination will also be provided.

#### 8.4.4.2 Brief neurological examination

A brief neurological examination will be performed throughout the study, according to the tabular schedule of study procedures.

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

Clinically significant neurological findings will be reported as AEs.

A listing of neurological examination findings from the brief neurological examination will also be provided. No summaries of these results are planned.

### 8.4.5 Vagus nerve stimulation

VNS status is recorded throughout the study, according to the tabular schedule of study procedures, only for those study participants with an implanted VNS device.

A listing of VNS status will be provided only for those study participants with an implanted VNS device.

### 8.4.6 Tanner stage assessment

Tanner stage will be assessed throughout the study, according to the tabular schedule of study procedures.

The investigator or qualified designee will evaluate the subject's sexual development using the 3-item Tanner scale (ie, for females: breasts, pubic hair, and overall stage; and for males: genitals, pubic hair, and overall stage). The investigator should use clinical judgment in deciding which study participants are selected for evaluation of Tanner Stage (ie, those study participants who are pubescent at screening or those study participants who become pubescent during the course of the study). The investigator will only report the overall score on the Tanner Stage CRF/eCRF module and this will be used for the associated summaries and listings.

A shift table will be produced showing the change in overall Tanner stage (1-5) from Baseline to Last Visit, by gender.

### 8.4.7 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This will be completed according to the tabular schedule of study procedures.

For study participants ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All study participants enrolling directly in SP848 and who are ≥6 years of age will complete the Baseline/Screening version of the C-SSRS at Visit 1 and will complete the Since Last Visit version at subsequent visits. If a subject becomes 6 years of age during the study, the Already Enrolled version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and use the Since Last Visit version at subsequent visits.

The C-SSRS is not validated and will not be used for study participants <6 years of age. For those study participants, signs and symptoms of depression will be assessed at each visit.

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

### 8.4.8 Achenbach Child Behavior Checklist (CBCL)

The Achenbach CBCL will be completed according to the tabular schedule of study procedures, only in countries where a validated translated version is available.

The Achenbach CBCL form is a questionnaire intended to evaluate a child's competencies and behavioral/emotional problems. Depending on the subject's age, 1 of 2 versions of the Achenbach CBCL is used. The CBCL/1½-5 is intended for use in children 18 months to 5 years and 11 months of age. For study participants ≥6 years to ≤18 years, the CBCL/6-18 will be used.

The same scale will be completed by the parent(s)/legal representative(s).

The CBCL/1½-5 comprises 100 questions and the CBCL/6-18 comprises 120 questions. In both questionnaires, the occurrence of certain problems and behaviors (in the past 2 months for the CBCL/1½-5 version and in the past 6 months for the CBCL/6-18 version) will be scored on the following scale:

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

The CBCL/1½-5 items will be grouped according to syndrome scales in Table 8–3 and the CBCL/6-18 items will be grouped according to empirically based syndrome scales in Table 8–4. For each syndrome, a raw score will be calculated as the sum of the considered item scores.

**Table 8–3: CBCL/1½-5**

| Syndrome scale | Items |
|---|---|
| Aggressive behavior | 8, 15, 16, 18, 20, 27, 29, 35, 40, 42, 44, 53, 58, 66, 69, 81, 85, 88, 96 |
| Anxious/depressed | 10, 33, 37, 43, 47, 68, 87, 90 |

### Table 8–3: CBCL/1½-5

| Syndrome scale | Items |
|---|---|
| Attention problems | 5, 6, 56, 59, 95 |
| Emotionally reactive | 21, 46, 51, 79, 82, 83, 92, 97, 99 |
| Sleep problems | 22, 38, 48, 64, 74, 84, 94 |
| Somatic complaints | 1, 7, 12, 19, 24, 39, 45, 52, 78, 86, 93 |
| Withdrawn | 2, 4, 23, 62, 67, 70, 71, 98 |
| Other problems | 3, 9, 11, 13, 14, 17, 25, 26, 28, 30, 31, 32, 34, 36, 41, 49, 50, 54, 55, 57, 60, 61, 63, 65, 72, 73, 75, 76, 77, 80, 89, 91, 100 |

### Table 8–4: CBCL/6-18

| Syndrome scale | Items |
|---|---|
| Aggressive behavior | 3, 16, 19, 20, 21, 22, 23, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104 |
| Anxious/depressed | 14, 29, 30, 31, 32, 33, 35, 45, 50, 52, 71, 91, 112 |
| Attention problems | 1, 4, 8, 10, 13, 17, 41, 61, 78, 80 |
| Rule-breaking behavior | 2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106 |
| Social problems | 11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79 |
| Somatic complaints | 47, 49, 51, 54, 56a, 56b, 56c, 56d, 56e, 56f, 56g |
| Thought problems | 9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100 |
| Withdrawn/depressed | 5, 42, 65, 69, 75, 102, 103, 111 |

Standardized T-scores are determined for each subject's raw syndrome and overall scores based on the subject's age and sex. Tables mapping each raw score to the appropriate T-score are provided in the CBCL Professional Manual. Standardized T-scores determined from each subject's raw syndrome scale scores will be reproduced programmatically using the spreadsheets "c15group2-probscales18moto5yrs" and "cbcgroup2-probscales6to18".

Raw scores and change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Raw scores and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

The Calculated T-scores, raw scores, and change from Baseline in raw scores will be listed.

A decrease from Baseline (change from Baseline <0) in the CBCL syndrome raw score will indicate improvement in behavior, while an increase (change from Baseline > 0) indicates worsening.

In addition, for both the CBCL/1½-5 syndrome and /6-18 syndrome, subjects will be categorized according to the Calculated T-score as follows:

- T-score is < 65 = "Normal"
- T-score is ≥ 65 = "Borderline or Clinical range (BCR)"

Summaries of shifts from Baseline to each post-Baseline visit, and from Baseline to Last Visit will also be provided based on the CBCL calculated T-score categories of Normal and BCR. The descriptive summaries of change from Baseline and shift summaries will be presented only when a corresponding Baseline value is available.

### 8.4.9 BRIEF-P and BRIEF assessment

The BRIEF-P/BRIEF assessments will be completed according to the tabular schedule of study procedures, only in countries where a validated translated version is available.

The BRIEF-P and BRIEF are validated tools that will be used for the evaluation of study participants ≥2 to <5 years of age, and ≥5 to ≤18 years of age, respectively.

#### 8.4.9.1 BRIEF-P scores

The BRIEF-P form comprises 63 questions with entry options N (never: scored as 1 point), S (sometimes: scored as 2 points), and O (often: scored as 3 points).

The 63 items are included in the raw Global Executive Composite (GEC) score which ranges from 63 to 189, with higher scores reflecting poorer functioning.

The 3 subscale scores and 5 individual component scores that make up these subscale scores are outlined in Table 8–5.

**Table 8–5: BRIEF-P questionnaire scoring**

| Scale/Index | Questions |
|---|---|
| Inhibit | 3, 8, 13, 18, 23, 28, 33, 38, 43, 48, 52, 54, 56, 58, 60, 62 |
| Shift | 5,10, 15, 20, 25, 30, 35, 40, 45, 50 |
| Emotional Control | 1, 6, 11, 16, 21, 26, 31, 36, 41, 46 |
| **Inhibitory self-control** | **All from {Inhibit and Emotional Control}** |
| **Flexibility** | **All from {Shift and Emotional Control}** |
| Working Memory | 2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 51, 53, 55, 57, 59, 61, 63 |
| Plan/Organize | 4, 9, 14, 19, 24, 29, 34, 39, 44, 49 |

**Table 8–5: BRIEF-P questionnaire scoring**

| Scale/Index | Questions |
|---|---|
| **Emergent metacognition** | **All from {Working Memory and Plan/Organize}** |
| **GEC Score** | **1-63** |

GEC=Global Executive Composite

Standardized T-scores are determined from each subject's raw GEC, inhibitory self-control, flexibility, emergent metacognition, and component scores. Tables that map each raw score to the appropriate T-score are provided in the BRIEF-P Professional Manual. Standardized T-scores determined from each subject's raw GEC score, subscale scores and 5 individual component scores will be produced programmatically using the spreadsheet "briefp-tscores".

T-score values and change from Baseline for the three index scores, the GEC and the 5 individual component scores for the BRIEF-P questionnaire will be summarized for each visit, and Last Visit.

The Calculated T-scores, raw scores, and changes from Baseline in raw scores will be listed.

A decrease from Baseline (change from Baseline <0) in the BRIEF-P syndrome raw score will indicate improvement in behavior, while an increase (change from Baseline > 0) indicates worsening.

In addition, for BRIEF-P, subjects will be categorized according to the Calculated T-score as follows:

- T-score is $< 65$ = "Normal"
- T-score is $\geq 65$ = "Elevated"

Summaries of shifts from Baseline to each post-Baseline visit, and from Baseline to Last Visit will also be provided based on BRIEF-P calculated T-score categories of Normal and Elevated.

The descriptive summaries of change from Baseline and shift summaries will be presented only when a corresponding Baseline value is available.

All BRIEF-P assessment data will be listed.

#### 8.4.9.2 BRIEF scores

The BRIEF form comprises 86 questions with entry options N (never: scored as 1 point), S (sometimes: scored as 2 points), and O (often: scored as 3 points).

The first 72 items are included in the GEC score which ranges from 72 to 216, with higher scores reflecting poorer functioning.

The 2 subscale scores and 8 individual component scores that make up these subscale scores are outlined in Table 8–6.

**Table 8–6: BRIEF questionnaire scoring**

| Scale/Index | Questions |
|---|---|
| Inhibit | 38, 41, 43, 44, 49, 54, 55, 56, 59, 65 |

### Table 8–6: BRIEF questionnaire scoring

| Scale/Index | Questions |
|---|---|
| Shift | 5, 6, 8, 12, 13, 23, 30, 39 |
| Emotional Control | 1, 7, 20, 25, 26, 45, 50, 62, 64, 70 |
| **Behavioral Regulation Index (BRI)** | **All from {Inhibit, Shift, and Emotional Control}** |
| Initiate | 3, 10, 16, 47, 48, 61, 66, 71 |
| Working Memory | 2, 9, 17, 19, 24, 27, 32, 33, 37, 57 |
| Plan/Organize | 11, 15, 18, 22, 28, 35, 36, 40, 46, 51, 53, 58 |
| Organization of Materials | 4, 29, 67, 68, 69, 72 |
| Monitor | 14, 21, 31, 34, 42, 52, 60, 63 |
| **Metacognition Index (MI)** | **All from {Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor}** |
| **GEC Score** | **1-72** |

The BRI score is the total of 28 items and ranges from 28-84. The MI score is the total of 44 items and ranges from 44 to 132.

T-score values and change from Baseline for the two indexed scores (BRI and MI), the GEC and the 8 individual component scores for the BRIEF questionnaire will be summarized for each visit, and Last Visit.

Standardized T-scores determined from each subject's raw GEC score, subscale scores and 8 individual component scores will be produced programmatically using scoring spreadsheet "brief-tscores". The Standardized T-scores, raw scores, and changes from Baseline in raw scores will be listed.

A decrease from Baseline (change from Baseline <0) in the BRIEF scores indicates improvement, while an increase (change from Baseline > 0) indicates worsening.

In addition, for BRIEF, subjects will be categorized according to the Calculated T-score as follows:

- T-score is < 65 = "Normal"
- T-score is ≥ 65 = "Elevated"

Summaries of shifts from Baseline to each post-Baseline visit, and from Baseline to Last Visit will also be provided based on BRIEF calculated T-score categories of Normal and Elevated.

The descriptive summaries of change from Baseline and shift summaries will be presented only when a corresponding Baseline value is available.

All BRIEF assessment data will be listed.

### 8.4.10 Bayley-III assessment

The Bayley-III assessments will be completed according to the tabular schedule of study procedures for study participants <18 months of age at study entry if enrolled in English-speaking countries.

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for this study.

The same scale will be completed for children from 1 month to <18 months of age enrolled in English-speaking countries.

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

The sum of scaled scored entered on the CRF/eCRF module, and the change from Baseline for the scales, as well as the general adaptive composite sum scaled score, will be summarized for each visit, and Last Visit.

All Bayley-III assessment data will be listed.

### 8.4.11 Medical procedures

Subjects who had any concomitant medical procedures during the study based on the Concomitant Medical Procedures eCRF module will be listed. Additionally, subjects who had any procedures or surgeries prior to study entry based on the Procedure History CRF/eCRF module will also be listed.

## 8.5 Palatability and ease of use questionnaires

UCB has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg, taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

The number and percentage of study participants who respond to each of the categories presented for the following questionnaires will be summarized at each visit it is assessed:

- Tablet palatability and ease of use
- Oral solution palatability and ease of use

Summaries will be performed overall and by seizure classification group (as defined in Section 3.2.12), with percentages based on the number of study participants with non-missing responses for the specified visit. All palatability and ease of use questionnaire data will be listed.

# 9 PHARMACOKINETICS

All study PK outcomes will be summarized for the PK-PPS.

Blood samples for LCM PK will be completed according to the tabular schedule of study procedures, for the assessment of LCM and concomitant AED plasma concentrations. These blood samples will be collected along with the clinical chemistry/hematology samples at any time after intake of LCM.

## 9.1 Descriptive statistics

Descriptive summaries (n, mean, SD, geometric mean, CV, geometric CV, median, minimum, and maximum) for the LCM plasma concentration and the plasma concentrations for selected concomitant AEDs will be presented by visit, timepoint and actual dose.

# 10 EFFICACY ANALYSES

The study efficacy variables include seizure counts (assessed using seizure diaries in order to evaluate the preliminary efficacy of LCM in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, and quality of life assessments (PedsQL and health care resource use).

All study efficacy variables will be summarized for the FAS, overall and repeated by efficacy seizure classification subgroup (where applicable), using the levels defined in Section 3.2.12. All summaries of efficacy data are descriptive; no statistical testing will be performed.

All efficacy variables will be listed.

## 10.1 Seizure counts

At Screening of SP847 (or other LCM pediatric clinical studies in epilepsy) or at the Screening Visit of SP848 (for study participants who directly enrolled into SP848) study participants/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous 4 weeks; this will serve as a historical Baseline. After the subject is enrolled in the SP848 study, seizure data will be collected in diaries provided to study participants/caregivers (including parents/legal guardians). Each subject/caregiver (including parent/legal guardian) will keep a diary to note daily seizure activity throughout the current study. The subject/caregiver (including parent/legal guardian) should be reminded to bring the diary with them at each clinic visit. The following information will be recorded:

- Seizure type
- Seizure frequency

Each seizure code in the clinical database will be mapped to exactly 1 of the ILAE seizure codes based on the 1981 ILAE classification (Seizure Count CRF/eCRF module).

Determination of Baseline Period seizures will be made utilizing both the historical Baseline and the seizure diary data collected from the date of the Screening Visit to the day prior to the date of first dose of LCM.

### 10.1.1 Seizure frequency per 28 days

For study participants with POS, seizure frequency per 28 days (as defined in Section 3.2.13) will be summarized descriptively and presented graphically.

Observed values and change from Baseline during the Titration Period, Post-Titration Period and the overall Treatment Period for the direct enrollers, overall Treatment Period for rollover study and overall Treatment Period for all study participants will be presented.

### 10.1.2 Percent change from Baseline in 28-day partial-onset seizure frequency

For study participants with POS, descriptive statistics for percent change from Baseline (as defined in Section 3.2.14) in 28-day seizure frequency will be presented. Any subject with seizure data during the time interval will be included in the summary for that seizure time interval.

Descriptive statistics will also be presented for percent change from Baseline in 28-day seizure frequency during the Titration Period, Post-Titration Period and for the overall Treatment Period for direct enrollers, for the overall Treatment Period for the rollover study participants and for the overall Treatment Period for all study participants.

Descriptive statistics for percent change from Baseline in 28-day seizure frequency during the Treatment Period will also be presented by seizure type (simple partial, complex partial, secondarily generalized) for POS. Only study participants who experienced a seizure type during the Baseline Period will be included in the analysis for that seizure type with only the seizure frequencies of that seizure type being used in the analysis.

Descriptive statistics for percent change from Baseline to each time interval in 28-day seizure frequency during the Treatment Period will also be presented. Any subject with seizure data during the time interval will be included in the summary for that seizure time interval and by seizure type.

The percent change from Baseline in 28-day seizure frequency among completer cohorts (as defined in Section 3.2.19) will also be presented.

### 10.1.3 ≥50% reduction in 28-days partial-onset seizure frequency

For study participants with POS, the number and percentage with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders) will be summarized by seizure time intervals (as defined in Section 3.2.21) and by seizure type (simple partial, complex partial, secondarily generalized). Any subject with seizure data during the time interval will be included in the summary for that seizure time interval and by seizure type.

### 10.1.4 ≥75% reduction in 28-days partial-onset seizure frequency

The analyses described in Section 10.1.3 for ≥50% reduction in 28-days partial-onset seizure frequency will also be performed for study participants with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders).

### 10.1.5 Seizure days per 28 days (subjects with generalized seizures only)

For study participants with generalized seizures, the number of seizure days per 28 days (as defined in Section 3.2.16) will be summarized descriptively during the treatment period.

### 10.1.6 Seizure-free status

The number and percentage of study participants achieving a seizure-free status (as defined in Section 3.2.18) will be presented for overall treatment period. This will be presented by completer cohorts (as defined in Section 3.2.19).

The number and percentage of study participants seizure-free among completer cohorts (as defined in Section 3.2.19) will also be presented separately by seizure type (simple partial, complex partial, secondarily generalized) for subjects with POS.

Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21). The number and percentage of study participants with seizure-free status at the end of each time interval during the treatment period will be presented separately by seizure type (simple partial, complex partial, secondarily generalized) for POS.

## 10.2 Global Impression of Change

### 10.2.1 Clinical Global Impression of Change

The Clinical Global Impression of Change is a 7-point categorical rating scale in which the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed at least once per year and will be completed according to the tabular schedule of study procedures.

The number and percentage of study participants by Clinical Global Impression of Change value will be summarized by visit and Last Visit. The denominator for the percentage calculation will be based on the number of study participants with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of study participants with non-missing values.

Clinical Global Impression of Change data will be listed.

### 10.2.2 Caregiver Global Impression of Change

The Caregiver Global Impression of Change is a 7-point categorical rating scale in which the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed at least once per year and will be completed according to the tabular schedule of study procedures.

The number and percentage of study participants by Caregiver Global Impression of Change value will be summarized by visit and Last Visit. The denominator for the percentage calculation will be based on the number of study participants with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section

3.2.8. The denominator for the percentage calculation will be based on the number of study participants with non-missing values.

Caregiver Global Impression of Change data will be listed.

## 10.3 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. The PedsQL will be completed up to two time per year and will be assessed according to the tabular schedule of study procedures. The Section 3.2.22 details how the scores for the core domains are calculated.

### 10.3.1 Pediatric Quality of Life Inventory Ages for ≤24 Months

The multidimensional PedsQL ≤24 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score (all items), the psychosocial health summary score, the physical health summary score and each of the 5 scale scores will be summarized for each visit and for Last Visit. All changes from baseline will only be calculated for visits when the subject uses the same form of the questionnaire as administered at baseline.

All PedsQL ≤24 months data will be listed.

### 10.3.2 Pediatric Quality of Life Inventory Ages >2 years

The multidimensional PedsQL >2years generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score (all items), the psychosocial health summary score, the physical health summary score and each of the 4 scale scores will be summarized for each visit and for Last Visit. All changes from baseline will only be calculated for visits when the subject uses the same form of the questionnaire as administered at baseline. All PedsQL >2years data will be listed.

## 10.4 Health care resource use

For health care resource use parameters, the following will be evaluated: concomitant medical procedures, health care provider consultations not foreseen by the protocol, and hospitalization/ER visits. Health care resource use parameters will be collected according to the tabular schedule of study procedures. Summaries will be presented during the Treatment Period.

### 10.4.1 Healthcare provider consultations

The number of healthcare provider consultations per subject 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.

The number of healthcare provider consultations during the Treatment Period will be summarized by type of provider (General Practitioner, Specialist Physician, Nurse, or Other).

Percentages will be relative to the number of healthcare provider consultations during the Treatment Period.

All healthcare provider consultations data will be listed.

### 10.4.2 Hospital stays and ER visits

The number of hospital stays per subject 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 study 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 3.2.23) 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 CRF/eCRF module where ER is marked as initial entry point will be defined as an ER visit. An ER visit with a subject transfer to an inpatient general ward will also be counted as a hospitalization. However, all other instances of ER visits (where subject 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 study 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. Study 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.

# 11 REFERENCES

This section is not applicable for this study.

# 12 APPENDICES

## 12.1 Marked abnormality criteria for laboratory data

### 12.1.1 Marked abnormality criteria for hematology data

**Table 12–1: Hematology abnormality criteria**

| Parameter | Age Range | Unit (conventional) | Abnormality criteria (conventional unit) | Unit (standard) | Abnormality criteria (standard unit) |
|---|---|---|---|---|---|
| Hematocrit | <2y | % | ≤27<br>>45 | % | ≤27<br>>45 |
| | 2y - <17y | % | ≤29<br>>47 | % | ≤29<br>>47 |
| | ≥17y | % | ≤85% of LLN<br>≥115% of ULN | % | ≤85% of LLN<br>≥115% of ULN |
| Hemoglobin | <2y | g/dL | ≤9.0<br>>15.0 | g/L | ≤90<br>>150 |
| | 2y - <17y | g/dL | ≤9.5<br>>16.0 | g/L | ≤95<br>>160 |
| | ≥17y | g/dL | ≤85% of LLN<br>≥115% of ULN | g/L | ≤85% of LLN<br>≥115% of ULN |
| WBC/ Leukocytes | All | $10^9$/L | ≤3.0<br>≥16.0 | G/L | ≤3.0<br>≥16.0 |
| Lymphocytes Absolute | <2y | $10^9$/L | <1.0<br>>9.8 | G/L | <1.0<br>>9.8 |
| | 2y - <6y | $10^9$/L | <0.7<br>>6.9 | G/L | <0.7<br>>6.9 |
| | ≥6y | $10^9$/L | <0.6<br>>5.0 | G/L | <0.6<br>>5.0 |
| Basophils | >1m | % | ≥5.0 | % | ≥5.0 |
| Basophils Absolute | >1m | $10^9$/L | ≥0.4 | G/L | ≥0.4 |
| Eosinophils | >1m | % | ≥10 | % | ≥10 |
| Eosinophils Absolute | >1m | $10^9$/L | ≥1.0 | G/L | ≥1.0 |
| Monocytes | >1m | % | ≥20.0 | % | ≥20.0 |

## Table 12–1: Hematology abnormality criteria

| Parameter | Age Range | Unit (conventional) | Abnormality criteria (conventional unit) | Unit (standard) | Abnormality criteria (standard unit) |
|---|---|---|---|---|---|
| Monocytes Absolute | >1m | $10^9$/L | ≥2.0 | G/L | ≥2.0 |
| Neutrophils Absolute | >1m | $10^9$/L | <1.5 | G/L | <1.5 |
| Platelets | >1m | $10^9$/L | ≤100<br>≥600 | G/L | ≤100<br>≥600 |
| RBC/ Erythrocytes | <2y | $10^{12}$/L | <3.0 | T/L | <3.0 |
| | ≥2y | $10^{12}$/L | <3.5 | T/L | <3.5 |

Abbreviations: ANC=absolute neutrophil count; m=months, y=years. A month is defined as 28 days; a year is defined as 365.25 days.

### 12.1.2 Marked abnormality criteria for chemistry data

**Table 12–2: Chemistry abnormality criteria**

| Parameter | Age Range | Unit (conventional) | Abnormality criteria (conventional unit) | Unit (standard) | Abnormality criteria (standard unit) |
|---|---|---|---|---|---|
| AST (SGOT) | All | U/L | ≥3.0 x ULN<br>≥5.0 x ULN<br>≥10.0 x ULN | U/L | ≥3.0 x ULN<br>≥5.0 x ULN<br>≥10.0 x ULN |
| ALT (SGPT) | All | U/L | ≥3.0 x ULN<br>≥5.0 x ULN<br>≥10.0 x ULN | U/L | ≥3.0 x ULN<br>≥5.0 x ULN<br>≥10.0 x ULN |
| Alkaline Phosphatase | <4y | U/L | ≥690 | U/L | ≥690 |
| | 4y - <10y | U/L | ≥834 | U/L | ≥834 |
| | 10y - <17y | U/L | ≥1761 | U/L | ≥1761 |
| | ≥17y | U/L | ≥3.0 x ULN | U/L | ≥3.0 x ULN |
| GGT | <6m | U/L | ≥522 | U/L | ≥522 |
| | 6m - <1y | U/L | ≥279 | U/L | ≥279 |
| | 1y - <13y | U/L | ≥66 | U/L | ≥66 |
| | 13y - <17y | U/L | ≥126 | U/L | ≥126 |
| | ≥17y | U/L | ≥3.0 x ULN | U/L | ≥3.0 x ULN |
| Total Bilirubin | >1m | mg/dL | ≥2.0 | umol/L | ≥34.208 |
| Total Protein | 2m-<1y | g/dL | <3.0<br>>11.9 | g/L | <30<br>>119 |
| | 1y - <17y | g/dL | <4.3<br>>12.0 | g/L | <43<br>>120 |
| | ≥17y | g/dL | <4.3<br>>13.0 | g/L | <43<br>>130 |
| Albumin | <1y | g/dL | <1.6<br>>7.2 | g/L | <16<br>>72 |
| | ≥1y - <17y | g/dL | <2.4<br>>8.4 | g/L | <24<br>>84 |
| | ≥17y | g/dL | <2.6 | g/L | <26 |
| BUN | <1y | mg/dL | ≥24 | mmol/L | ≥8.568 |
| | 1y - <17y | mg/dL | ≥36 | mmol/L | ≥12.852 |

## Table 12–2: Chemistry abnormality criteria

| Parameter | Age Range | Unit (conventional) | Abnormality criteria (conventional unit) | Unit (standard) | Abnormality criteria (standard unit) |
|---|---|---|---|---|---|
| | ≥17y | mg/dL | ≥40 | mmol/L | ≥14.28 |
| Urea | <1y | mg/dL | >42 | mmol/L | >7.014 |
| | ≥1y | mg/dL | >60 | mmol/L | >10.02 |
| Creatinine | 1y - <10y | mg/dL | >1.2 | umol/L | >106.8 |
| | 10y - <16y | mg/dL | >1.8 | umol/L | >159.12 |
| | ≥16y | mg/dL | ≥2.0 | umol/L | ≥176.8 |
| Creatinine Clearance[a b] | All | mL/min | <50 | mL/s | <0.835 |
| Bicarbonate | >1m - <17y | mEq/L | <15<br>>38 | mmol/L | <15<br>>38 |
| | ≥17y | mEq/L | <18<br>>38 | mmol/L | <18<br>>38 |
| Calcium | <1y | mg/dL | <6.9<br>>12.2 | mmol/L | <1.725<br>>3.05 |
| | 1y - <17y | mg/dL | <7.4<br>>11.7 | mmol/L | <1.85<br>>2.925 |
| | ≥17y | mg/dL | ≤7.6<br>≥11.0 | mmol/L | ≤1.9<br>≥2.75 |
| Chloride | >1m | mEq/L | ≤90<br>≥112 | mmol/L | ≤90<br>≥112 |
| Phosphorous | <1y | mg/dL | <1.8<br>>8.2 | mmol/L | <0.5814<br>>2.6486 |
| | 1y - <17y | mg/dL | <1.8<br>>7.4 | mmol/L | <0.5814<br>>2.3902 |
| | ≥17y | mg/dL | ≤2.0<br>≥6.0 | mmol/L | ≤0.646<br>≥1.938 |
| Potassium | <1y | mEq/L | ≤3.0<br>≥6.5 | mmol/L | ≤3.0<br>≥6.5 |
| | ≥1y | mEq/L | ≤3.0<br>≥6.0 | mmol/L | ≤3.0<br>≥6.0 |

## Table 12–2: Chemistry abnormality criteria

| Parameter | Age Range | Unit (conventional) | Abnormality criteria (conventional unit) | Unit (standard) | Abnormality criteria (standard unit) |
|---|---|---|---|---|---|
| Sodium | >1m | mEq/L | <127<br>>151 | mmol/L | <127<br>>151 |
| Glucose | >1m - <17y | mg/dL | <50<br>≥180 | mmol/L | <2.775<br>≥9.99 |
| | ≥17y | mg/dL | <50<br>≥200 | mmol/L | <2.775<br>≥11.1 |
| Total Cholesterol | ≥1y | mg/dL | >250 | mmol/L | >6.475 |
| LDL (calculated) | 1y - <17y | mg/dL | >140 | mmol/L | >3.626 |
| | ≥17y | mg/dL | >200 | mmol/L | >5.18 |
| HDL | ≤2y | mg/dL | <10 | mmol/L | <0.259 |
| | >2y | mg/dL | <20 | mmol/L | <0.518 |
| Triglycerides | <1y | mg/dL | >150 | mmol/L | >8.475 |
| | ≥1y | mg/dL | >300 | mmol/L | >3.39 |
| Uric Acid | <1y | mg/dL | >7.7 | umol/L | >457.996 |
| | 1y - <13y | mg/dL | >6.5 | umol/L | >386.62 |
| | 13y - <17y | mg/dL | >8.6 | umol/L | >511.528 |
| | ≥17y | mg/dL | >9.5 | umol/L | >565.06 |
| Thyroxine (T4) | <1y | ug/dL | ≤4.3<br>≥18.4 | nmol/L | ≤55.3453<br>≥236.8264 |
| | ≥1y | ug/dL | ≤3.8<br>≥13.5 | nmol/L | ≤48.9098<br>≥173.7585 |
| Globulin | <1y | g/dL | <1.0<br>>4.5 | g/L | <10<br>>45 |
| | ≥1y | g/dL | <1.2<br>>5.3 | g/L | <12<br>>53 |

Abbreviations: ALT= alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; dL=deciliter; GGT: gamma-glutamyl transferase; HDL=high density lipoprotein; LDL=low density lipoprotein; L=liter; m=months (a month is defined as 28 days) mg=milligram; mmol=millimoles; µg=microgram; U=unit; ULN=upper limit of normal; y=years (a year is defined as 365.25 days)

[a]Schwartz equation (study participants <12): Cr Cl ml/min=[Height (cm) * 0.55] / serum creatinine

[b] Cockroft equation (study participants >12): Male: Cr Cl ml/min=[(140-age) x body weight (kg)] / (72 x serum creatinine); Female: Cr Cl ml/min=[(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85

## 12.2 Other Significant TEAEs

The following MedDRA PTs are defined as other significant TEAEs.

**Table 12–3: Other significant TEAEs**

| MedDRA Preferred Term |
|---|
| **CARDIAC AND ECG RELATED TERMS** |
| Atrial conduction time prolongation |
| Atrial fibrillation |
| Atrial flutter |
| Atrioventricular block second degree |
| Atrioventricular block third degree |
| Atrioventricular dissociation |
| Bradyarrhythmia |
| Bradycardia |
| Cardiac arrest |
| Cardiac pacemaker insertion |
| Cardiac fibrillation |
| Cardiac flutter |
| Conduction disorder |
| Heart Rate decreased |
| Implantable defibrillator insertion |
| Sick sinus syndrome |
| Sinus arrest |
| Sinus bradycardia |
| Torsade de pointes |

### Table 12–3: Other significant TEAEs

| MedDRA Preferred Term |
|---|
| Ventricular asystole |
| Ventricular fibrillation |
| Ventricular flutter |
| Ventricular tachycardia |
| Ventricular tachyarrhythmia |
| **SUICIDALITY RELATED TERMS** |
| Completed suicide |
| Depression suicidal |
| Intentional overdose |
| Intentional self-injury |
| Multiple drug overdose intentional |
| Poisoning deliberate |
| Suicidal behaviour |
| Suicidal ideation |
| Suicide attempt |
| Self injurious behaviour |
| Self-injurious ideation |
| **ADDITIONAL TERMS** |
| Abnormal behaviour |
| Appetite disorder |
| Decreased appetite |
| Diet refusal |

**Table 12–3: Other significant TEAEs**

| MedDRA Preferred Term |
|---|
| Food aversion |
| Hypophagia |
| Loss of consciousness |
| Syncope |

## 12.3 AEs for Potentially Drug Induced Liver Injury (PDILI)

The following MedDRA PTs are defined as AEs for Potentially Drug Induced Liver Injury:

**Table 12–4: 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 |
| Coma hepatic |
| Cryptogenic cirrhosis |

**Table 12–4: AEs for PDILI**

| |
|---|
| 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 |

**Table 12–4: AEs for PDILI**

| |
|---|
| Jaundice hepatocellular |
| Liver disorder |
| Liver injury |
| Mixed liver injury |
| Non-alcoholic steatohepatitis |
| Ocular icterus |
| Subacute hepatic failure |



# 13 AMENDMENTS TO THE STATISTICAL ANALYSIS PLAN

## 13.1 Amendment 1

**Rationale for the amendment**

The primary purpose of this substantial amendment is for consistency with other SAPs and protocols in the LCM pediatric program.

**Specific changes**

**Change #1**

SAP/Amendment Number and Date

Final SAP 27 Apr 2015

**Has been changed to:**

SAP – Amendment 1 18 Dec 2015

**Change #2**

List of Abbreviations

Cmax has been deleted.

**Change #3**

**Section 3.2.4 Study visit labeling**

Visits will be labeled in table summaries (according to the schedule outlined in Section 16.1 of the protocol) as follows:

- "Screening Visit" for subjects who directly enrolled into SP848

- "Titration Visit X" for scheduled visits during titration for subjects who directly enrolled into SP848
- "Visit X, Week X (Descriptor)" for other scheduled visits during the Treatment Period

Listings will also include "Unscheduled Visit" as applicable.

**Has been changed to:**

Visits will be labeled in table summaries (according to the schedule outlined in Section 16.1 of the protocol) as follows:

- "Screening Visit" for subjects who directly enrolled into SP848
- "Titration Visit X" for scheduled visits during titration for subjects who directly enrolled into SP848
- "Visit X, Week X" for other scheduled visits during the Treatment Period
- "Last Visit" (see below in Section 3.2.6 for further information)

Listings will also include "Unscheduled Visit" as applicable.

**Change #4**

**Section 3.2.5 Monthly time intervals**

A month is defined as 28 days and time intervals based on monthly durations are defined as multiples of 28 days (eg, 12 months is defined as 336 days).

**Has been changed to:**

A month is defined as 28 days and time intervals based on monthly durations are defined as multiples of 28 days (eg, 12 months is defined as 336 days). A subject is included in the analysis for a 3-month interval if they are exposed to LCM at any time during that time interval.

**Change #5**

**Section 3.2.18 Seizure-free status**

Subjects will be considered seizure-free for a given period if the subject completes the period, reports zero seizures during the period, and have no more than 10% of days in the period for which seizure data is not available (ie, "not done" is noted on the Seizure Frequency CRF/eCRF module). Seizure diary days where "not done" has been reported for days when subjects were participating in a previous study will not be counted toward the 10% of days with missing seizure diary data (eg, missing seizure data due to a previous study will not count against a subject in the assessment of seizure-free status).

**Has been changed to:**

Subjects will be considered seizure-free for a given period if the subject completes the period, reports zero seizures during the period, and have no more than 10% of days in the period for which seizure data is not available (ie, "not done" is noted on the Seizure Frequency CRF/eCRF module). Seizure diary days where "not done" has been reported for days when subjects were participating in a previous study will not be counted toward the 10% of days with missing seizure diary data (eg, missing seizure data due to a previous study will not count against a

subject in the assessment of seizure-free status). If a subject enrolls in the EP0060 iv study, days of participation in EP0060 will also not be considered in the assessment of seizure-free status.

Change #6

Section 3.5.1 Safety Set

The Safety Set (SS) will consist of all subjects who meet the inclusion/exclusion criteria, sign an informed consent form, and take at least 1 dose of LCM in SP848. This is the primary analysis set.

Has been changed to:

The Safety Set (SS) will consist of all enrolled subjects who took at least 1 dose of LCM in this study. All safety analyses will be performed on the SS.

**Change #7**

**Section 3.5.1 Full Analysis Set**

The FAS will consist of all subjects from the SS who had a Baseline seizure frequency assessment and at least 1 post-Baseline assessment from SP848 of seizure frequency data.

**Has been changed to:**

The FAS will be used for the analysis of seizure data and will consist of all subjects in the SS, who have at least 1 completed post-Baseline seizure diary.

**Change #8**

**Section 3.9.4 Analysis sets**

The protocol-defined PK-PPS has been updated to the text shown in Section 3.5.2.

The FAS (defined in Section 3.5.3) has been added to the list of analysis sets for this study.

**Has been changed to:**

The protocol-defined SS has been updated to the text shown in Section 3.5.1 to clarify that all enrolled subjects who take at least one dose of LCM will be included.

The protocol-defined PK-PPS has been updated to the text shown in Section 3.5.2.

The FAS (defined in Section 3.5.3) has been added to the list of analysis sets for this study.

**Change #9**

**Section 5.1 Subject disposition**

The number of subjects screened, in addition to the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure, will be presented.

A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of subjects screened, number of subjects enrolled, and the number of subjects in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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

- The number of screened subjects
- The number and percentage of enrolled subjects
- The number and percentage of subjects in the SS
- The number and percentage of subjects in the PK-PPS
- The number and percentage of subjects in the FAS

Additionally, a summary of disposition and discontinuation reasons will present the following for all screened subjects, and those in the SS (overall and repeated by weight band and disposition enrollment group using the levels defined in Section 3.2.10 and (previously described in Section 3.2.12.2) respectively), PK-PPS, and FAS:

The number and percentage of subjects starting the study

The number and percentage of subjects completing the study (defined as subjects who have 'Completed subject' selected as status at termination – see Study Termination eCRF module)

The number and percentage of subjects completing 12, 24, 36 and >36 months of the study

The overall number and percentage of subjects discontinuing and the number and percentage of subjects discontinuing by primary reason for discontinuation. If the subject discontinued the study and the Study Termination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of subjects enrolled under each protocol amendment (estimated by date of informed consent) will be presented, separately, for global protocols prior to version 5.1 and for Japanese direct enrollers. This will also be presented in the subject data listings.

**Has been changed to:**

The number of subjects screened, in addition to the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure, will be presented.

A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of subjects screened, number of subjects enrolled, and the number of subjects in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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

- The number of screened subjects
- The number and percentage of enrolled subjects

- The number and percentage of subjects in the SS
- The number and percentage of subjects in the PK-PPS
- The number and percentage of subjects in the FAS

Additionally, a summary of disposition and discontinuation reasons will present the following for all subjects in the SS (overall and repeated by weight band and disposition enrollment group using the levels defined in Section 3.2.10 and (previously described in Section 3.2.12.1) respectively, PK-PPS, and FAS:

The number and percentage of subjects starting the study

The number and percentage of subjects completing the study (defined as subjects who have 'Completed subject' selected as status at termination – see Study Termination eCRF module)

The number and percentage of subjects completing 12, 24, 36 and >36 months of the study

The overall number and percentage of subjects discontinuing and the number and percentage of subjects discontinuing by primary reason for discontinuation. If the subject discontinued the study and the Study Termination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of subjects enrolled under each protocol amendment (estimated by date of informed consent) will be presented, separately, for global protocols prior to version 5.1 and for Japanese direct enrollers. This will also be presented in the subject data listings.

**Change #10**

**Section 6.1 Demographics and other Baseline characteristics**

Demographic variables, unless otherwise specified, will be obtained from the demographics data collected at the time of entry into the previous pediatric LCM study for those subjects who enrolled from SP847 (or other LCM pediatric clinical studies in epilepsy). Demographic variables will be obtained from the Screening Visit for those subjects who directly enrolled into SP848.

Demographic variables will be presented by weight band (using the levels defined in Section 3.2.10), by demographic enrollment group (using the levels previously defined in Section 3.2.12.2) and overall for the SS. The variables to be considered are:

- Age at entry into previous pediatric study (years) (as defined in 3.2.9) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years - <18 years)
- Age at entry into SP848 (years) (as defined in Section 3.2.9)
- Gender
- Weight (kg)
- Weight band (as defined in Section 3.2.10)
- Height (cm)

- BMI (kg/m$^2$) (as defined in Section 3.2.11)
- 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)

A listing of reproductive potential and birth control measures will be provided. No summaries of these results are planned.

**Has been changed to:**

Demographic variables, unless otherwise specified, will be obtained from the demographics data collected at the time of entry into the previous pediatric LCM study for those subjects who enrolled from SP847 (or other LCM pediatric clinical studies in epilepsy). Demographic variables will be obtained from the Screening Visit for those subjects who directly enrolled into SP848.

Demographic variables will be presented by weight band (using the levels defined in Section 3.2.10), by demographic enrollment group (using the levels previously defined in Section 3.2.12.2)) and overall for the SS. The variables to be considered are:

Age at entry into previous pediatric study for subjects from SP847 and age at entry into SP848 for directly enrolled subjects (years) (as defined in 3.2.9) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years - <18 years)

- Age at entry into SP848 (years) (as defined in Section 3.2.9)
- Gender
- Weight (kg)
- Weight band (as defined in Section 3.2.10)
- Height (cm)
- BMI (kg/m$^2$) (as defined in Section 3.2.11)
- 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)
- Vagus nerve stimulation (VNS) use (Active VNS, No VNS, and VNS not active)

A listing of reproductive potential and birth control measures will be provided. No summaries of these results are planned.

**Change #11**

**Section 6.4.1 Number of Previous AEDs**

**Has been changed to:**

**Section 6.4.1 Number of previous AEDs**

**Change #12**

**Section 6.4.2 Number of concomitant AEDs taken at the start of the SP848 Treatment Period**

The number of concomitant AEDs taken at the start of the SP848 Treatment Period will be summarized for the SS based on the following categorization: 1 AED, 2 AEDs, and 3 AEDs.

**Section 6.4.3 Concomitant AEDs taken at the start of the SP848 Treatment Period**

The number and percentage of subjects taking concomitant AEDs at the start of the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

**Has been changed to:**

**Section 6.4.2 Concomitant AEDs taken at the start of the SP848 Treatment Period**

Concomitant AEDs taken at the start of the SP848 Treatment Period are defined as AEDs taken concomitantly with LCM at the time of first dose of LCM in SP848.

The number of concomitant AEDs taken at the start of the SP848 Treatment Period will be summarized for the SS based on the following categorization: 1 AED, 2 AEDs, and 3 AEDs. The number and percentage of subjects taking concomitant AEDs at the start of the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

**Change #13**

**Section 6.4.4 Concomitant AEDs**

The number and percentage of subjects taking concomitant AEDs during the Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

Vagus nerve stimulation (VNS) is allowed and will not be counted as a concomitant AED.

**Has been changed to:**

Section 6.4.3 Concomitant AEDs taken during the SP848 Treatment Period

Concomitant AEDs taken during the SP848 Treatment Period are defined as AEDs taken concomitantly for at least one day in common with LCM in SP848.

The number and percentage of subjects taking concomitant AEDs during the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

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

**Change #14**

**Section 6.4.5 Concomitant medications (excluding AEDs)**

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

**Has been changed to:**

**Section 6.4.4 Concomitant medications (excluding AEDs)**

The number and percentage of subjects taking concomitant non-AEDs during the SP848 Treatment Period will be summarized overall and, separately, by WHODD anatomical main group (level 1) and therapeutic subgroup (level 2), for the SS.

**Change #15**

**Section 8.2 Adverse events**

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and demographic enrollment group using the levels defined in Section 3.2.10 and previously described in Section 3.2.12.2, respectively. The number and percentage of subjects 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 28 days after last dose of LCM will be considered treatment emergent. Post-treatment AEs are defined as AEs which had an onset date after 28 days after the last dose of LCM.

All AEs reported during the study including pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of subjects with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and previously described in Section 3.2.12.2, respectively.

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 TEAEs leading to discontinuation
- Incidence of TEAEs by relationship to LCM
- Incidence of TEAEs by maximum intensity
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM

- Incidence of non-serious TEAEs occurring in at least 5% of subjects
- Incidence of non-serious TEAEs occurring in at least 5% of subjects by relationship to LCM
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2.)

The following summaries of AEs will also be repeated by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and previously described in Section 3.2.12.2, respectively.

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of non-serious TEAEs occurring in at least 5% of subjects
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2))

In addition, summaries for the incidence of TEAEs overall, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation, and incidence of other significant TEAEs will be repeated presenting the site and subject number of all those subjects experiencing each TEAE as well as in subject data listings.

**Has been changed to:**

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and previously described in Section 3.2.12.2, respectively. Additional tables will also be presented by time interval using the definition in Section 3.2.5. The number and percentage of subjects 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 30 days after last dose of LCM 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 pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if

applicable), and the number and percentage of subjects with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and demographic enrollment group using the levels defined in Section 3.2.10 and previously described in Section 3.2.12.2, respectively.

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 TEAEs leading to discontinuation

Incidence of TEAEs by relationship to LCM

Incidence of TEAEs by maximum intensity

Incidence of non-serious TEAEs by relationship to LCM

Incidence of fatal TEAEs by relationship to LCM

Incidence of non-serious TEAEs occurring in at least 5% of subjects

Incidence of non-serious TEAEs occurring in at least 5% of subjects by relationship to LCM

Incidence of drug-related TEAEs by seriousness

Incidence of other significant TEAEs (defined in Appendix 12.1)

The following summaries of AEs will also be repeated by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and previously described in Section 3.2.12.2, respectively.

Incidence of TEAEs

Incidence of serious TEAEs

Incidence of TEAEs leading to discontinuation

Incidence of non-serious TEAEs occurring in at least 5% of subjects

Incidence of drug-related TEAEs by seriousness

Incidence of other significant TEAEs (defined in Appendix 12.1)

The following summaries of AEs will be presented for the time intervals (using the definition in Section 3.2.5) of: <=3 months, >3 to <=6 months, >6 to <=9 months, >9 to <=12 months, >12 to <=15 months, >15 to <=18 months, >18 to <=21 months, >21 to <=24 months, and >=24 months:

Incidence of all TEAEs with onset during the Treatment Period

Incidence of all serious TEAEs with onset during the Treatment Period

Incidence of all TEAEs leading to discontinuation with onset during the Treatment Period

Incidence of all other significant TEAEs with onset during the Treatment Period (defined in Appendix 12.2)

In addition, summaries for the incidence of TEAEs overall, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation, and incidence of other significant TEAEs will be repeated presenting the site and subject number of all those subjects experiencing each TEAE as well as in subject data listings.

**Change #16**

**Section 8.3 Clinical laboratory evaluations**

Hematology, blood chemistry (including liver function tests), urinalysis, and endocrinology parameters are assessed throughout the study, according to the tabular schedules of study procedures. Urinalysis will be performed for subjects ≥5 years of age only.

All summaries of laboratory parameters will only summarize parameters planned based on the protocol. However, both planned and unplanned laboratory parameters will be provided in subject data listings. Summaries will include hematology, chemistry and endocrinology results; urinalysis results will be included in subject data listings only.

Observed values of hematology, chemistry, and endocrinology parameters will be summarized for each visit and Last Visit. Change from Baseline for hematology, chemistry, and endocrinology parameters will be summarized for all post-Baseline visits, and Last Visit.

A shift table that cross-tabulates Baseline versus maximum result during the Treatment Period in categories of <1 x ULN (upper limit of normal), 1 to <2 x ULN, 2 to <3 x ULN, ≥3 x ULN, and missing will be presented for liver function tests (LFT) which include ALT, AST, GGT, Total Bilirubin, and Alkaline Phosphatase.

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values during the defined Treatment Period at scheduled or unscheduled visits which occur on or after the first SP848 LCM administration through to the end of the study but were normal at Baseline.

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value will be summarized, at each post-Baseline visit and Last Visit. Percentages will be relative to the number of subjects with a value at each time point. Criteria for determining if a value is TEMA are detailed in Appendix 12.1.

Serum and urine pregnancy test will be performed on all females of childbearing potential, according to the tabular schedule of study procedures.

A listing of serum and urine pregnancy test results will be provided. No summaries of these results are planned.

**Has been changed to:**

Hematology, blood chemistry (including liver function tests), urinalysis, and endocrinology parameters are assessed throughout the study, according to the tabular schedules of study procedures. Urinalysis will be performed for subjects ≥5 years of age only.

All summaries of laboratory parameters will only summarize parameters planned based on the protocol. However, both planned and unplanned laboratory parameters will be provided in subject data listings. Summaries will include hematology, chemistry, and endocrinology results; urinalysis results will be included in subject data listings only.

Observed values of hematology, chemistry, and non-gender specific endocrinology parameters (i.e. thyroid stimulating hormone, triiodothyronine [total and serum-free], and thyroxine [total and serum-free]) will be summarized for each visit and Last Visit. Change from Baseline for hematology, chemistry, and non-gender specific endocrinology parameters will be summarized for all post-Baseline visits, and Last Visit. Gender specific endocrinology parameters (i.e. follicle stimulating hormone, luteinizing hormone, and testosterone) will be presented similarly, by gender.

A shift table that cross-tabulates Baseline versus maximum result during the Treatment Period in categories of <1 x ULN (upper limit of normal), 1 to <2 x ULN, 2 to <3 x ULN, ≥3 x ULN, and missing will be presented for liver function tests (LFT) which include ALT, AST, GGT, Total Bilirubin, and Alkaline Phosphatase.

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values during the defined Treatment Period at scheduled or unscheduled visits which occur on or after the first SP848 LCM administration through to the end of the study but were normal at Baseline.

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value will be summarized, at each post-Baseline visit and Last Visit. Percentages will be relative to the number of subjects with a value at each time point. Criteria for determining if a value is TEMA are detailed in Appendix 12.1.

Serum and urine pregnancy testing will be performed on all females of childbearing potential, according to the tabular schedule of study procedures.

Serum and urine pregnancy test results will be listed. No summaries of these results are planned.

**Change #17**

**Section 8.4.2 Electrocardiograms (ECGs)**

Standard 12-lead ECGs (2 interpretable recordings [20 to 30 minutes apart]) will be performed throughout the study, according to the tabular schedule of study procedures.

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

ECGs will be reviewed locally and at a central ECG laboratory. If any abnormal finding is assessed by the investigator to be clinically significant, then the ECG should be repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

For ECGs, Baseline will be defined as the average of all pre-dose interpretable readings. For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

Observed values of ECG results will be summarized for each visit and Last Visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits, and Last Visit. This will be summarized overall and repeated by weight band using the levels defined in Section 3.2.10.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, will be summarized for all visits, and Last Visit. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each time point based on the worst observed outcome across all abnormalities reported at that time point.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit will also be provided based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant.

A listing of ECG data will be provided for all subjects with other significant TEAEs in the Cardiac and ECG Related Terms category defined in Appendix 12.2. A subject data listing of all ECG parameter values for all subjects will also be presented. Listings will include results from each recording and the average of all recordings.

The number and percentage of subjects with treatment-emergent ECG abnormalities will be presented for each post-Baseline visit and Last Visit. Abnormalities reported at an unscheduled visit will be summarized under the scheduled visit preceding the unscheduled visit (if the abnormality was not present already at the preceding scheduled visit). Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline. All ECG parameter values will be listed for subjects meeting any abnormality criteria.

Abnormality criteria to be used in the determination of ECG abnormalities are defined as follows, where increase and decrease are relative to Baseline values:

**Table 8-2: ECG abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| QT interval (ms) | 1m - <12y | ≥500 |
| | ≥12y | ≥500 or ≥60ms increase from Baseline |
| QTc(F) (ms) | <6m | >490, or >15% increase from Baseline |
| | 6m - <3y | >440, or >15% increase from Baseline |
| | 3y - <12y | >440, or >15% increase from Baseline |
| | ≥12y - <17y | >440, or >15% increase from Baseline |
| | ≥17y | ≥500 or ≥60ms increase from Baseline |
| QTc(B) (ms) | <6m | >490, or >15% increase from Baseline |

**Table 8-2: ECG abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| | 6m - <3y | >450, or >15% increase from Baseline |
| | 3y - <12y | >450, or >15% increase from Baseline |
| | ≥12y - <17y | >450, or >15% increase from Baseline |
| | ≥17y | ≥500 or ≥60ms increase from Baseline |
| PR interval (ms) | <6m | >150, or ≥25% increase from Baseline |
| | 6m - <3y | >170, or ≥25% increase from Baseline |
| | 3y - <12y | >180, or ≥25% increase from Baseline |
| | ≥12y - <17y | >200, or ≥25% increase from Baseline |
| | ≥17y | Treatment-emergent value >200, >220, >250 |
| QRS interval (ms) | <6m | >90, or ≥25% increase from Baseline |
| | 6m - <3y | >90, or ≥25% increase from Baseline |
| | 3y - <12y | >100, or ≥25% increase from Baseline |
| | ≥12y - <17y | ≥110, or ≥25% increase from Baseline |
| | ≥17y | Treatment-emergent value >100, >120, >140 |
| Heart rate (bpm) | <6m | <100, >180 |
| | 6m - <3y | <90, >150 |
| | 3y - <12y | <60, >130 |
| | ≥12y | <50, >120 |

Abbreviations: bpm=beats per minute; m=months; ms=milliseconds; QTc=corrected QT interval; y=years. A month is defined as 28 days; a year is defined as 365.25 days.

A subject data listing will be provided that identifies subjects with a clinically significant finding after the first dose of LCM for each type of ECG abnormality.

**Has been changed to:**

Standard 12-lead ECGs (2 interpretable recordings [20 to 30 minutes apart]) will be performed throughout the study, according to the tabular schedule of study procedures.

For ECGs, Baseline will be defined as the average of all pre-dose interpretable readings. For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

Observed values of ECG results will be summarized for each visit and Last Visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits, and Last Visit. This will be summarized overall and repeated by weight band using the levels defined in Section 3.2.10.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, will be summarized for all visits, and Last Visit. Percentages will be relative to the number of subjects with an ECG assessment at each visit. Subjects are counted at most once at each visit based on the worst observed outcome across all abnormalities reported at that visit.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit will also be provided based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant.

A listing of ECG data will be provided for all subjects with other significant TEAEs in the Cardiac and ECG Related Terms category defined in Appendix 12.2. A subject data listing of all ECG parameter values for all subjects will also be presented. Listings will include results from each recording and the average of all recordings.

The number and percentage of subjects with treatment-emergent ECG abnormalities will be presented for each post-Baseline visit and Last Visit. Abnormalities reported at an unscheduled visit will be summarized under the scheduled visit preceding the unscheduled visit (if the abnormality was not present already at the preceding scheduled visit). Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline. All ECG parameter values will be listed for subjects meeting any abnormality criteria.

Abnormality criteria to be used in the determination of ECG abnormalities are defined as follows, where increase and decrease are relative to Baseline values:

**Table 8-2: ECG abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| QT interval (ms) | 1m - <12y | ≥500 |
| | ≥12y | ≥500 or ≥60ms increase from Baseline |
| QTc(F) (ms) | <6m | >490, or >15% increase from Baseline |
| | 6m - <3y | >440, or >15% increase from Baseline |
| | 3y - <12y | >440, or >15% increase from Baseline |
| | ≥12y - <17y | >440, or >15% increase from Baseline |
| | ≥17y | ≥500 or ≥60ms increase from Baseline |
| QTc(B) (ms) | <6m | >490, or >15% increase from Baseline |
| | 6m - <3y | >450, or >15% increase from Baseline |
| | 3y - <12y | >450, or >15% increase from Baseline |
| | ≥12y - <17y | >450, or >15% increase from Baseline |
| | ≥17y | ≥500 or ≥60ms increase from Baseline |

**Table 8-2: ECG abnormality criteria**

| Parameter | Age Range | Abnormality Criteria |
|---|---|---|
| PR interval (ms) | <6m | >150, or ≥25% increase from Baseline |
| | 6m - <3y | >170, or ≥25% increase from Baseline |
| | 3y - <12y | >180, or ≥25% increase from Baseline |
| | ≥12y - <17y | >200, or ≥25% increase from Baseline |
| | ≥17y | Treatment-emergent value >200, >220, >250 |
| QRS interval (ms) | <6m | >90, or ≥25% increase from Baseline |
| | 6m - <3y | >90, or ≥25% increase from Baseline |
| | 3y - <12y | >100, or ≥25% increase from Baseline |
| | ≥12y - <17y | ≥110, or ≥25% increase from Baseline |
| | ≥17y | Treatment-emergent value >100, >120, >140 |
| Heart rate (bpm) | <6m | <100, >180 |
| | 6m - <3y | <90, >150 |
| | 3y - <12y | <60, >130 |
| | ≥12y | <50, >120 |

Abbreviations: bpm=beats per minute; m=months; ms=milliseconds; QTc=corrected QT interval; y=years. A month is defined as 28 days; a year is defined as 365.25 days.

A subject data listing will be provided that identifies subjects with a clinically significant finding after the first dose of LCM for each type of ECG abnormality.

**Change #18**

**Section 8.4.2 Vagus nerve stimulation**

VNS status is recorded throughout the study, according to the tabular schedule of study procedures, only for those subjects with an implanted VNS device.

A listing of VNS status will be provided only for those subjects with an implanted VNS device. No descriptive summaries of these results are planned.

**Has been changed to:**

VNS status is recorded throughout the study, according to the tabular schedule of study procedures, only for those subjects with an implanted VNS device.

A listing of VNS status will be provided only for those subjects with an implanted VNS device.

**Change #19**

### Section 8.4.9.1 BRIEF-P scores

The BRIEF-P form comprises 63 questions with entry options N (never: scored as 1 point), S (sometimes: scored as 2 points), and O (often: scored as 3 points).

The 63 items are included in the raw Global Executive Composite (GEC) score which ranges from 63 to 189, with higher scores reflecting poorer functioning.

The 2 subscale scores and 5 individual component scores that make up these subscale scores are outlined in Table 8-5.

**Table 8-5: BRIEF-P questionnaire scoring**

| **Scale/Index** | **Questions** |
|---|---|
| Inhibit | 3, 8, 13, 18, 23, 28, 33, 38, 43, 48, 52, 54, 56, 58, 60, 62 |
| Shift | 5,10, 15, 20, 25, 30, 35, 40, 45, 50 |
| Emotional Control | 1, 6, 11, 16, 21, 26, 31, 36, 41, 46 |
| **BRI** | **All from {Inhibit, Shift, and Emotional Control}** |
| Working Memory | 2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 51, 53, 55, 57, 59, 61, 63 |
| Plan/Organize | 4, 9, 14, 19, 24, 29, 34, 39, 44, 49 |
| **MI** | **All from {Working Memory and Plan/Organize}** |
| **GEC Score** | **1-63** |

BRI=Behavioral Regulation Index, MI=Metacognition Index, GEC=Global Executive Composite

Standardized T-scores are determined from each subject's raw GEC, BRI, MI, and component scores. Tables that map each raw score to the appropriate T-score are provided in the BRIEF-P Professional Manual and will be reproduced programmatically.

Calculated T-score values and change from Baseline for the two indexed scores (BRI and MI) and GEC for the BRIEF-P questionnaire will be summarized for each visit, and Last Visit.

All BRIEF-P assessment data will be listed.

**Has been changed to:**

The BRIEF-P form comprises 63 questions with entry options N (never: scored as 1 point), S (sometimes: scored as 2 points), and O (often: scored as 3 points).

The 63 items are included in the raw Global Executive Composite (GEC) score which ranges from 63 to 189, with higher scores reflecting poorer functioning.

The 3 subscale scores and 5 individual component scores that make up these subscale scores are outlined in Table 8-5.

| Table 8-5: BRIEF-P questionnaire scoring | |
|---|---|
| **Scale/Index** | **Questions** |
| Inhibit | 3, 8, 13, 18, 23, 28, 33, 38, 43, 48, 52, 54, 56, 58, 60, 62 |
| Shift | 5,10, 15, 20, 25, 30, 35, 40, 45, 50 |
| Emotional Control | 1, 6, 11, 16, 21, 26, 31, 36, 41, 46 |
| **Inhibitory self-control** | **All from {Inhibit and Emotional Control}** |
| **Flexibility** | **All from {Shift and Emotional Control}** |
| Working Memory | 2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 51, 53, 55, 57, 59, 61, 63 |
| Plan/Organize | 4, 9, 14, 19, 24, 29, 34, 39, 44, 49 |
| **Emergent metacognition** | **All from {Working Memory and Plan/Organize}** |
| **GEC Score** | **1-63** |

GEC=Global Executive Composite

Standardized T-scores are determined from each subject's raw GEC, inhibitory self-control, flexibility, emergent metacognition, and component scores. Tables that map each raw score to the appropriate T-score are provided in the BRIEF-P Professional Manual and will be reproduced programmatically.

Calculated T-score values and change from Baseline for the three indexed scores and GEC for the BRIEF-P questionnaire will be summarized for each visit, and Last Visit.

All BRIEF-P assessment data will be listed.

**Change #20**

**Section 10.3 Pediatric Quality of Life Inventory (PedsQL)**

The multidimensional PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

(defined in Section 3.2.22) will be summarized for each visit and for Last Visit.

All PedsQL data will be listed.

**Has been changed to:**

**Section 10.2.3 Pediatric Quality of Life Inventory (PedsQL)**

The multidimensional PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score and each of the 4 scale scores (defined in Section 3.2.22) will be summarized for each visit and for Last Visit. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8.

All PedsQL data will be listed.

**Change #21**

**Section 10.4 Health care resource use**

**Section 10.4.1 Medical procedures**

**Section 10.4.2 Healthcare provider consultations**

**Section 10.4.3 Hospital stays and ER visits**

**Section 10.4.4 Palatability and ease of use questionnaires**

**Have been changed to:**

**Section 10.2.4 Health care resource use**

**Section 10.2.4.1 Medical procedures**

**Section 10.2.4.2 Healthcare provider consultations**

**Section 10.2.4.3 Hospital stays and ER visits**

**Section 10.2.5 Palatability and ease of use questionnaires**

## 13.2 Amendment 2

**Rationale for the amendment**

The primary purpose of this substantial amendment is for consistency with other SAPs and protocols in the LCM pediatric program and to incorporate Japan and China specific protocols.

Specific changes

**Change #1**

SAP/Amendment Number and Date

Final SAP 27 Apr 2015

SAP – Amendment 1 18 Dec 2015

Has been changed to:

Final SAP 27 Apr 2015

SAP – Amendment 1 18 Dec 2015

SAP – Amendment 2 8 Mar 2019

**Change #2**

General Change throughout the document: "enrollment groups" has been changed to "seizure categories subgroups".

**Change #3**

List of Tables

**Has been changed to:**

Added Table 12-3 Other significant TEAEs and Table 12-4 AEs for PDILI

**Change #4**

List of Abbreviations

**Has been changed to:**

PDILI Potential Drug Induced Liver Injury has been added

**Change #5**

**Section 2.1.3 Other objectives**

- To allow subjects who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow subjects who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM

- Protocol Amendment 5.3 (specific to Japan) allows approximately 46 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM to directly enroll at approximately 9 sites in Japan

**Has been changed to:**

To allow subjects who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM

- To allow subjects who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM
- Protocol Amendment 5.3 (specific to Japan) allows approximately 46 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM to directly enroll at approximately 9 sites in Japan
- Protocol Amendment 5.4 (specific to China) allows approximately 60 additional pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years who have not previously received LCM to directly enroll in China
- Protocol Amendment 6 allows approximately 75 additional eligible pediatric subjects with epilepsy who participated in EP0060 to receive LCM

**Change #6**

Section 2.3.1.1 Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy

**Has been changed to:**

Section 2.3.1.1 Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy (rollover subjects)

**Change #7**

**Section 2.3.1.2 Subjects enrolling directly into SP848**

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control. Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator with the exception of subjects in Japan. For sites in Japan, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children or until the sponsor decides to discontinue the development of LCM in children in Japan.

The same study conditions described in Section 2.5.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

**Has been changed to**

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously received LCM will be permitted to enroll directly into SP848.

Beginning with Protocol Amendment 5.3 (specific to Japan), approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll at approximately 9 sites in Japan. Beginning with Protocol Amendment 5.4 (specific to China), approximately 60 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll in China.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control. Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator with the exception of subjects in Japan. For sites in Japan, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children or until the sponsor decides to discontinue the development of LCM in children in Japan.

The same study conditions described in Section 2.5.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

**Change #8**

**Section 2.3.2 Tabular schedule of study procedures**

The schedule of study procedures for SP848 (Year 1, Year 2, and Year 3) is provided in Section 16.1 of the protocol.

**Has been changed to**

The schedule of the study procedures for SP848 are provided in Section 16.1 of the study protocol and country specific protocol amendments for Japan and China.

**Change #9**

**Section 2.4 Determination of sample size**

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

**Has been changed to**

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. For sites in China, approximately 60 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly in to SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

**Change #10**

**Section 3.1 General presentation of summaries and analyses**

All summaries, unless otherwise stated below, will be presented overall for all subjects and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥1 to <6 months
- ≥6 months to <1 year
- ≥1 to <2 years
- ≥2 to <4 years
- Total <4 years
- ≥4 to <12 years
- 12 to <16 years
- Total ≥4 to <16 years
- ≥16 years

Summaries for Japan direct enrollers only well be presented overall for all applicable subjects and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥4 to <12 years
- ≥12 to <16 years
- Total ≥4 to <16 years
- ≥16 years

**Has been changed to**

All summaries, unless otherwise stated below, will be presented overall for all subjects and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥1 month to <4 years

- ≥4 to <12 years
- ≥12 to <16 years
- Total ≥4 to <16 years
- ≥16 years

**Change #11**

**Section 3.1 General presentation of summaries and analyses**

Summaries for BRIEF-P will be presented overall for all applicable subjects and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥2 to <4 years
- ≥4 to <5 years

**Has been changed to**

Summaries for BRIEF-P will be presented overall for all applicable subjects and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥2 to <4 years
- ≥4 to <6 years

**Change #12**

**Section 3.2.2 Study Periods**

This study consists of a Treatment Period and a Post-Treatment Period.

Treatment Period

This is defined as the period of time from the date of first dose of LCM in SP848 to the latter of the last LCM dose date and the study Termination Visit date.

Post-Treatment 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 Clinic Visit or last contact with the subject.

**Has been changed to:**

This study consists of a Treatment Period and a Post-Treatment Period.

Treatment Period

This is defined as the period of time from the date of first dose of LCM in SP848 to the latter of the last LCM dose date and the study Termination Visit (ie, Early Termination Visit) date.

The Treatment Period is further broken down into the Titration Period and the Post-Titration Period for direct enrollers:

Titration Period: defined as the date of the first dose of study medication to the day prior to date of Visit 1 or the date of Early Termination (ET) visit in the situation where a subject discontinues prior to the last visit in the Titration Period.

Post-Titration Period: defined as the date of Visit 1 to the end of the Treatment Period.

Post-Treatment 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 Clinic Visit or last contact with the subject.

**Change #13**

**Section 3.2.3 Mapping of assessments performed at Early Termination Visit**

Safety and efficacy assessments at an Early Termination Visit (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. Such assessments will also be considered for Last Visit.

In particular, assessments which are done at all visits during the Treatment Period (eg, vital signs, body weight and height), will have ETVs corresponding to a scheduled visit mapped to the corresponding scheduled visit.

**Has been changed to**

Safety and efficacy assessments at an Early Termination Visit (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. Such assessments will also be considered for Last Visit. Subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. For those subjects the ETV will be mapped to the next scheduled visit, ie, the assessments documented at Visit 13/ETV will be assigned to the next scheduled visit, for which the corresponding assessment is scheduled, following the last documented visit.

In particular, assessments which are done at all visits during the Treatment Period (eg, vital signs, body weight and height), will have ETVs corresponding to a scheduled visit mapped to the corresponding scheduled visit.

For subjects enrolled from sites in Japan, they are allowed to stay in the study longer than 2 years. Such subjects will have a separate ETV if they are in the study after Visit 13.

**Change #14**

**Section 3.2.7 Exposure duration**

The overall duration of LCM exposure for each subject 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, 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, and >24 months.

Subject-years of LCM exposure in the study is calculated as the duration of exposure (days) divided by 365.25. Subject-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, and >24 months, where 1 month is defined as 28 days.

**Has been changed to**

The overall duration of LCM exposure for each subject 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, 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.

Subject-years of LCM exposure in the study is calculated as the duration of exposure (days) divided by 365.25. Subject-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, where 1 month is defined as 28 days.

**Change #15**

**Section 3.2.12 Enrollment groups**

Enrollment groups

3.2.12.1 Disposition

Subjects will be classified as belonging to one of the following enrollment groups for the purpose of disposition subgroup analyses:

- SP847
- SP0966 (subjects with generalized epilepsy)
- Direct enrollers
- Japan direct enrollers

Demographics

Subjects will be classified as belonging to one of the following enrollment groups for the purpose of demographic subgroup analyses:

- POS subjects (combining subjects from SP847, direct enrollers into SP848 and Japan direct enrollers)
- SP0966 (subjects with generalized epilepsy)
- Direct enrollers
- Japan direct enrollers

3.2.12.2 Efficacy

Subjects will be classified as belonging to one of the following enrollment groups for the purpose of efficacy subgroup analyses:

- POS subjects (combining subjects from SP847, direct enrollers into SP848 and Japan direct enrollers)

- SP0966 (subjects with generalized epilepsy)
- Direct enrollers
- Japan direct enrollers

Exposure

Subjects will be classified as belonging to one of the following enrollment groups for the purpose of exposure subgroup analyses:

- POS subjects (combining subjects from SP847, direct enrollers into SP848 and Japan direct enrollers)
- SP0966 (subjects with generalized epilepsy)
- Direct enrollers
- Japan direct enrollers

**Has been changed to**

Seizure Classification Subgroups

Subjects will be classified as belonging to one of the following seizure classification subgroups based on their seizure classification history for the purpose of disposition, demographic, efficacy, and exposure subgroup analyses:

- POS subjects
  - Subjects from SP0966 who reported only Type I seizures
  - Subjects who reported any Type I seizure
- Generalized seizure subjects
  - Subjects from SP0966 unless they reported only Type I seizures
  - Subjects who reported only Type II seizures
- Unclassified
  - Subjects who reported only Type III seizures

**Change #16**

**Section 3.2.13 Seizure frequency**

Seizure frequency per 28 days (SF) will be based on the number of days (D) for which seizure information was provided:

SF = (Number of seizures) x (28/D)

If a seizure cluster is reported, it will be assigned to the correct seizure type and the highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event will be used as the imputed number of seizures for the day on which the cluster occurred. If no other seizures are recorded for that seizure type for the subject in the 28 days prior to the

cluster event, the frequency will be set to 1 or the number of cluster episodes reported if more than 1 cluster event occurred on the same day.

**Has been changed to:**

Seizure frequency per 28 days (SF) will be based on the number of days (D) for which seizure information was provided:

SF = (Number of seizures in the analysis period) x (28/D)

If a seizure cluster is reported, it will be assigned to the correct seizure type and the highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event will be used as the imputed number of seizures for the day on which the cluster occurred. If no other seizures are recorded for that seizure type for the subject in the 28 days prior to the cluster event, the frequency will be set to 1.

If more than 1 cluster event occurred on the same day for a Type II or Type III seizure, the seizure clusters will be assigned to the correct seizure type and the frequency for each cluster event will be set to the highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event. If no other seizures are recorded for that seizure type for the subject in the 28 days prior to the cluster event, the frequency will be set to the number of cluster episodes reported.

If more than 1 cluster event occurred on the same day for a Type I seizure, the seizure clusters will be assigned to the correct seizure type and the overall frequency will be set to the maximum of:

- The highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event
- The number of cluster episodes reported on that day

**Change #17**

**Section 3.2.15 Response to treatment**

Response to treatment is based on the percent change in seizure frequency relative to Baseline (using the Baseline definition in Section 3.3). Subjects who experience at least a 50% reduction from Baseline will be considered >=50% responders. Subjects who experience at least a 75% reduction from Baseline will be considered >=75% responders.

**Has been changed to**

Response to treatment is based on the percent change in seizure frequency relative to Baseline (using the Baseline definition in Section 3.3). Subjects who experience at least a 50% reduction from Baseline will be considered ≥50% responders. Subjects who experience at least a 75% reduction from Baseline will be considered ≥75% responders.

**Change #18**

**Section 3.2.21 Seizure time intervals**

Subjects will be classified as belonging to one of the following time intervals for the purpose of seizure efficacy analyses:

- ≤3 months
- >3 to ≤6 months
- >6 to ≤12 months
- >12 to ≤18 months
- >18 to ≤24 months
- ≥24 months

**Has been changed to**

Subjects will be classified as belonging to one of the following time intervals for the purpose of seizure efficacy analyses:

- ≤3 months
- >3 to ≤6 months
- >6 to ≤12 months
- >12 to ≤18 months
- >18 to ≤24 months
- >24 to ≤30 months
- >30 to ≤36 months
- >36 to ≤ 42 months
- > 42 to ≤48 months
- >48 months

**Change #19**

**Section 3.2.22 Pediatric Quality of Life Inventory (PedsQL)**

The PedsQL assessment is retrospective to the prior one month, and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: never, almost never, sometimes, often, or almost always). These scores of 0 to 4 will be transformed by the function: 100 – (response x 25) in order to generate scores of 0, 25, 50, 75, and 100 where a higher value represents a better health-related quality of life (HRQoL).

Each scale score is then calculated as the mean of the non-missing categorized items if 50% or more of the items are non-missing.

The above algorithm will also be used to calculate an overall total scale score (all scales) for each subject.

**Has been changed to**

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. The PedQL Measurement Model consists of developmentally appropriate forms for pediatric subjects

≥1 month to ≤12 months, ≥13 months to ≤24 months, >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. For each subject, the same version that is used at Baseline should be used for 12 months and thereafter the appropriate age versions should be used.

PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales:

- Physical Functioning
- Emotional Functioning
- Social Functioning
- School Functioning

The PedsQL assessment is retrospective to the prior one month, and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: never, almost never, sometimes, often, or almost always). These scores of 0 to 4 will be transformed by the function: 100 – (response x 25) in order to generate scores of 0, 25, 50, 75, and 100 where a higher value represents a better health-related quality of life (HRQoL).

Each scale score is then calculated as the mean of the non-missing categorized items if 50% or more of the items are non-missing.

The above algorithm will also be used to calculate an overall total scale score (all scales), and the psychosocial health summary score (a combination of the emotional, social and school functioning questions) for each subject.

**Change #20**

**Section 3.7 Center Pooling Strategy**

Except for the subgrouping of sites in Japan (see Section 3.2.12) no pooling of centers is planned for this study.

**Has been changed to:**

No pooling of centers is planned for this study.

**Change #21**

**Section 3.9.1 Study Variables**

The following primary variables, which are defined as only being assessed at Baseline in the protocol, will be assessed at all visits:

Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior.

Bayley-III scales for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)

**Has been changed to:**

Section deleted

**Change #22**

**Section 3.9.2 Clarification of efficacy variables for seizure counts**

The following efficacy variables, which are not been defined in the protocol, will be assessed:

- Percent change from Baseline in 28-day seizure frequency (as defined in Section 10.1.2)
- ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders as defined in Section 10.1.3)
- ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders as defined in Section 10.1.4)
- Seizure-free status (as defined in Section 10.1.5)
- Seizure days per 28 days (as defined in Sections 10.1.6)

**Has been changed to:**

The following efficacy variables, which are not defined in the protocol, will be assessed:

- Percent change from Baseline in 28-day seizure frequency (as defined in Section 10.1.2)
- Proportion of subjects with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders as defined in Section 10.1.3)
- Proportion of subjects with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders as defined in Section 10.1.4)
    - Seizure-free status (as defined in Section 10.1.5)
    - Seizure days per 28 days (as defined in Section 10.1.6)

**Change #23**

**Section 3.9.4 Analysis Sets**

The protocol-defined SS has been updated to the text shown in Section 3.5.1 to clarify that all enrolled subjects who take at least one dose of LCM will be included.

The protocol-defined PK-PPS has been updated to the text shown in Section 3.5.2.

The FAS (defined in Section 3.5.3) has been added to the list of analysis sets for this study.

**Has been changed to:**

Section deleted

**Change #24**

As a result of changes #22 and #24

**Section 3.9.1 Study variables**

**Section 3.9.2 Clarification of efficacy variables for seizure counts**

**Section 3.9.3 Treatment assignment and treatment groups**

**Section 3.9.4 Analysis sets**

**Section 3.9.5 Handling of dropouts or missing data**

**Section 3.9.6 Examination of subgroups**

**Have been changed to:**

**Section 3.9.1 Clarification of efficacy variables for seizure counts**

**Section 3.9.2 Treatment assignment and treatment groups**

**Section 3.9.3 Handling of dropouts or missing data**

**Section 3.9.4 Examination of subgroups**

**Change #25**

**Section 4.4 Multicenter studies**

Except for the subgroup analyses of sites in Japan (see Section 3.2.12), no multicenter analyses are planned; therefore, this section is not applicable for this study.

**Has been changed to:**

No multicenter analyses are planned; therefore, this section is not applicable for this study.

**Change #26**

**Section 5.1 Subject disposition**

The number of subjects screened, in addition to the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure, will be presented.

A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of subjects screened, number of subjects enrolled, and the number of subjects in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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

- The number of screened subjects
- The number and percentage of enrolled subjects
- The number and percentage of subjects in the SS
- The number and percentage of subjects in the PK-PPS
- The number and percentage of subjects in the FAS

Additionally, a summary of disposition and discontinuation reasons will present the following for all subjects in the SS (overall and repeated by weight band and disposition enrollment group using the levels defined in Sections 3.2.10 and 3.2.12.1 respectively), PK-PPS, and FAS:

The number and percentage of subjects starting the study

The number and percentage of subjects completing the study (defined as subjects who have 'Completed subject' selected as status at termination – see Study Termination eCRF module)

The number and percentage of subjects completing 12, 24, 36 and >36 months of the study

The overall number and percentage of subjects discontinuing and the number and percentage of subjects discontinuing by primary reason for discontinuation. If the subject discontinued the study and the StudyTermination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of subjects enrolled under each protocol amendment (estimated by date of informed consent) will be presented, separately, for global protocols prior to version 5.1 and for Japanese direct enrollers. This will also be presented in the subject data listings.

**Has been changed to:**

The number of subjects screened (screened subjects include subjects who signed an ICF), in addition to the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure, will be presented. A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of subjects screened, number of subjects enrolled, and the number of subjects in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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

- The number of screened subjects
- The number and percentage of enrolled subjects
- The number and percentage of subjects in the SS
- The number and percentage of subjects in the PK-PPS
- The number and percentage of subjects in the FAS
- The number of subjects from each parent study
- The number of original direct enrollers
- The number of Japanese direct enrollers
- The number of Chinese direct enrollers

Additionally, a summary of disposition and discontinuation reasons will present the following for all subjects in the SS (overall and repeated by weight band and seizure classification subgroups using the levels defined in Sections 3.2.10 and 3.2.12, respectively), PK-PPS, and FAS:

The number and percentage of subjects starting the study

The number and percentage of subjects completing the study (defined as subjects who have 'Completed subject' selected as status at termination – see Study Termination eCRF module)

The number and percentage of subjects completing 12, 24, 36 and >36 months of the study

The overall number and percentage of subjects discontinuing and the number and percentage of subjects discontinuing by primary reason for discontinuation. If the subject discontinued the study and the Study Termination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of subjects enrolled under each protocol amendment (estimated by date of informed consent) will be presented for all global protocols, and separately, for Chinese direct enrollers from version 5.4 and for Japanese direct enrollers from version 5.3. This will also be presented in the subject data listings.

**Change #27**

**Section 6.3.1 History of seizure types**

The number and percentage of subjects experiencing partial-onset seizures (type I), simple partial (type IA), complex partial (type IB), and partial, secondary generalized seizures (type IC), in addition to each seizure category within such, at any time prior to study entry (into the previous study for those subjects who enrolled from SP847 [or other LCM pediatric clinical studies in epilepsy] or into SP848 for those directly enrolled) will be summarized based on the International League Against Epilepsy (ILAE) Seizure Classification History CRF/eCRF module. This will be summarized for the SS, separately, for POS subjects (combining subjects from SP847, direct enrollers into SP848 and Japan direct enrollers) and for subjects from SP0966 with generalized seizures.

For POS subjects (combining subjects from SP847, direct enrollers into SP848 and Japan direct enrollers) the following classifications will be used. A subject will be classified as having a history of partial-onset seizures (I) if the subject has a history of simple partial (IA), complex partial (IB), or partial, secondary generalized (IC) seizures. A subject will be classified as having a history of simple partial seizures if the subject has a history of motor signs (IA1), somatosensory or special sensory symptoms (IA2), autonomic symptoms or signs (IA3), or psychic symptoms (IA4). A subject will be classified as having a history of complex partial seizures if the subject has a history of simple partial onset followed by impairment of consciousness with simple partial features (IB1a) or automatism (IB1b), or if the subject has a history of impairment of consciousness at onset with no other features (IB2a) or automatism (IB2b). A subject will be classified as having a history of partial, secondary generalized seizures if the subject has a history of simple partial evolving to generalized (IC1), complex partial evolving to generalized (IC2), or simple partial evolving to complex partial evolving to generalized (IC3) seizures.

For subjects from SP0966 with generalized seizures the following classifications will be used. A subject will be classified as having a history of partial-onset seizures (I) if the subject has a history of simple partial (IA), complex partial (IB), or partial, secondary generalized (IC) seizures. A subject will be classified as having a history of simple partial seizures if the subject

has a history of motor signs (IA1), somatosensory or special sensory symptoms (IA2), autonomic symptoms or signs (IA3), or psychic symptoms (IA4). A subject will be classified as having a history of generalized seizures (II) if the subject has a history of absence (IIA), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), or atonic (IIF) seizures. subject may also be

classified as having a history of unclassified epileptic seizures (III).

**Has been changed to:**

The number and percentage of subjects experiencing partial-onset seizures (type I), simple partial (type IA), complex partial (type IB), and partial, secondary generalized seizures (type IC), in addition to each seizure category within such, at any time prior to study entry (into the previous study for rollover subjects or into SP848 for those direct enrollers) will be summarized based on the 1981 International League Against Epilepsy (ILAE) Seizure Classification History CRF/eCRF module. This will be summarized for the SS, by seizure classification subgroups.

For POS subjects the following classifications will be used. A subject will be classified as having a history of partial-onset seizures (I) if the subject has a history of simple partial (IA), complex partial (IB), or partial, secondary generalized (IC) seizures. A subject will be classified as having a history of simple partial seizures if the subject has a history of motor signs (IA1), somatosensory or special sensory symptoms (IA2), autonomic symptoms or signs (IA3), or psychic symptoms (IA4). A subject will be classified as having a history of complex partial seizures if the subject has a history of simple partial onset followed by impairment of consciousness with simple partial features (IB1a) or automatism (IB1b), or if the subject has a history of impairment of consciousness at onset with no other features (IB2a) or automatism (IB2b). A subject will be classified as having a history of partial, secondary generalized seizures if the subject has a history of simple partial evolving to generalized (IC1), complex partial evolving to generalized (IC2), or simple partial evolving to complex partial evolving to generalized (IC3) seizures.

For subjects with generalized seizures the following classifications will be used. A subject will be classified as having a history of partial-onset seizures (I) if the subject has a history of simple partial (IA), complex partial (IB), or partial, secondary generalized (IC) seizures. A subject will be classified as having a history of simple partial seizures if the subject has a history of motor signs (IA1), somatosensory or special sensory symptoms (IA2), autonomic symptoms or signs (IA3), or psychic symptoms (IA4). A subject will be classified as having a history of generalized seizures (II) if the subject has a history of absence (IIA), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), or atonic (IIF) seizures. A subject may also be classified as having a history of unclassified epileptic seizures (III).

**Change #28**

**Section 6.3.2 History of seizure characteristics**

Quantitative summaries of epilepsy duration and age at diagnosis (as defined in Section 3.2.9)

will be summarized for the SS. This will be summarized, separately, for POS subjects (combining subjects from SP847, direct enroller into SP848 and Japan direct enrollers) and for subjects from SP0966 with generalized seizures.

**Has been changed to**

Quantitative summaries of epilepsy duration and age at diagnosis (as defined in Section 3.2.9) will be summarized for the SS. This will be summarized for the SS, by seizure classification subgroups.

**Change #29**

**Section 6.3.3 History of seizure counts**

The Historical Seizure Counts CRF/eCRF module records the number of seizures per pre-selected ILAE seizure code experienced by the subject during the 4 weeks prior to Baseline. These data will be provided in a subject data listing. This will be listed, separately, for POS subjects (combining subjects from SP847, direct enrollers into SP848 and Japan direct enrollers) and for subjects from SP0966 with generalized seizures.

**Has been changed to**

The Historical Seizure Counts CRF/eCRF module records the number of seizures per pre-selected ILAE seizure code experienced by the subject during the 4 weeks prior to Baseline. These data will be provided in a subject data listing. This will be summarized for the SS, by seizure classification subgroups.

**Change #30**

**Section 6.4 Prior and concomitant medications**

A listing of all medications taken during the study will be presented.

**Has been changed to**

All prior and concomitant medications will be presented by seizure classification subgroup, age group, weight band and overall. Antiepileptic drugs defined as medications documented on the "Concomitant Medications (AEDs only)" log form. A medical review will be performed to ensure that the medications are documented correctly. A listing of all medications taken during the study will be presented.

**Change #31**

**Section 8.1 Extent of Exposure**

The modal daily LCM dose (mg/kg/day), as defined in Section 3.2.8, will be summarized, overall, and repeated by weight band using the levels defined in Section 3.2.10. In addition, the number of subjects and subject-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 3.2.8.

**Has been changed to:**

The modal daily LCM dose (mg/kg/day), as defined in Section 3.2.8, will be summarized, overall, and repeated by weight band using the levels defined in Section 3.2.10. In addition, the number of subjects and subject-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 3.2.8.

Summary statistics (n, mean, standard deviation (SD), minimum and maximum) for the duration of LCM exposure (days) and median daily LCM dose (mg/kg/day) during each of the following analysis periods for direct enrollers: Titration, Post-Titration and Treatment Period will be summarized for the SS. Duration of LCM exposure (days) and median daily LCM dose

(mg/kg/day) for the Treatment Period will be summaries for the rollover and all subjects in the SS separately.

**Change #32**

**Section 8.2 Adverse events**

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and 3.2.12.2 respectively. Additional tables will also be presented by time interval using the definition in Section 3.2.5. The number and percentage of subjects 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 30 days after last dose of LCM 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 pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of subjects with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and 3.2.1.2.2 respectively.

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 TEAEs leading to discontinuation
- Incidence of TEAEs by relationship to LCM
- Incidence of TEAEs by maximum intensity
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of non-serious TEAEs occurring in at least 5% of subjects
- Incidence of non-serious TEAEs occurring in at least 5% of subjects by relationship to LCM

- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2)

The following summaries of AEs will also be repeated by weight band and demographic enrollment group using the levels defined in Sections 3.2.10 and 3.2.12.2 respectively.

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of non-serious TEAEs occurring in at least 5% of subjects
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2)

The following summaries of AEs will be presented for the time intervals (using the definition in Section 3.2.5) of: ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months, >12 to ≤15 months, >15 to ≤18 months, >18 to ≤21 months, >21 to ≤24 months, and ≥24 months:

- Incidence of all TEAEs with onset during the Treatment Period
- Incidence of all serious TEAEs with onset during the Treatment Period
- Incidence of all TEAEs leading to discontinuation with onset during the Treatment Period
- Incidence of all other significant TEAEs with onset during the Treatment Period (defined in Appendix 12.2)

In addition, summaries for the incidence of TEAEs overall, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation, and incidence of other significant TEAEs will be repeated presenting the site and subject number of all those subjects experiencing each TEAE as in subject data listings.

**Has been changed to:**

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively. Additional tables will also be presented by time interval using the definition in Section 3.2.5. The number and percentage of subjects 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 30 days after last dose of LCM 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 pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of subjects with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, the overall summary will be presented for the Titration Period, Post-Titration Period and Treatment Period for the direct enrollers and the Treatment Period for the rollover subjects.

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

- Incidence of TEAEs
- Incidence of TEAEs with onset during the Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Post-Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Treatment Period for direct enrollers
- Incidence of TEAEs for direct enrollers
- Incidence of TEAEs for rollover subjects
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of TEAEs by relationship to LCM
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs related to Potentially Drug Induced Liver Injury (PDILI)
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of non-serious TEAEs occurring in at least 5% of subjects
- Incidence of non-serious TEAEs occurring in at least 5% of subjects by relationship to LCM
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will also be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively.

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of non-serious TEAEs occurring in at least 5% of subjects

- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will be presented for the time intervals (using the definition in Section 3.2.5) of: ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months, >12 to ≤ 15 months, >15 to ≤18 months, >18 to ≤21 months, >21 to ≤24 months, and >24 to ≤ 30 months, >30 to ≤36 months, >36 to ≤42 months, >42 to ≤48 months, >48 months:

- Incidence of all TEAEs with onset during the Treatment Period
- Incidence of all serious TEAEs with onset during the Treatment Period
- Incidence of all TEAEs leading to discontinuation with onset during the Treatment Period
- Incidence of all other significant TEAEs with onset during the Treatment Period (defined in Appendix 12.2)

In addition, summaries for the incidence of TEAEs overall, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation, incidence of other significant TEAEs, and TEAEs related to PDILI will be repeated presenting the site and subject number of all those subjects experiencing each TEAE as well as in subject data listings.

**Change #33**

**Section 8.3 Clinical Laboratory evaluations**

Serum and urine pregnancy testing will be performed on all females of childbearing potential, according to the tabular schedule of study procedures.

Serum and urine pregnancy test results will be listed. No summaries of these results are planned.

**Has been changed to:**

Serum and urine pregnancy testing will be performed on all females of childbearing potential, according to the tabular schedule of study procedures.

Serum and urine pregnancy test results will be listed. No summaries of these results are planned.

Potential drug-induce liver injury (PDILI) IMP discontinuation criteria as outlined in the protocol, will be evaluated at all laboratory assessments. The number and percentage of subjects meeting PDILI criteria (ie, ALT or AST criteria and/or total bilirubin criteria, and/or presence of symptoms), will be presented by treatment group. Percentages will be based on the number of subjects with a non-missing measurement for the variable of interest at the relevant visit.

**Change #34**

**Section 8.4.7 Achenbach Child Behavior Checklist (CBCL)**

The Achenbach CBCL will be completed according to the tabular schedule of study procedures, only in countries where a validated translated version is available.

The Achenbach CBCL form is a questionnaire intended to evaluate a child's competencies and behavioral/emotional problems. Depending on the subject's age, 1 of 2 versions of the

Achenbach CBCL is used. The CBCL/1½-5 is intended for use in children 18 months to 5 years and 11 months of age. For subjects ≥6 years to ≤18 years, the CBCL/6-18 will be used.

The same scale will be completed at the Screening Visit (subjects directly enrolled into SP848), Visit 1 (subjects enrolled from SP847 or other pediatric clinical studies in epilepsy), and Visit 13/Termination Visit (or ETV) (all subjects) by the parent(s)/legal representative(s).

The CBCL/1½-5 comprises 100 questions and the CBCL/6-18 comprises 120 questions. In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

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

The CBCL/1½-5 will be grouped according to syndrome scales in Table 8-3 and the CBCL/6-18 will be grouped according to empirically based syndrome scales in Table 8-4.

**Has been changed to**

The Achenbach CBCL will be completed according to the tabular schedule of study procedures, only in countries where a validated translated version is available.

The Achenbach CBCL form is a questionnaire intended to evaluate a child's competencies and behavioral/emotional problems. Depending on the subject's age, 1 of 2 versions of the Achenbach CBCL is used. The CBCL/1½-5 is intended for use in children 18 months to 5 years and 11 months of age. For subjects ≥6 years to ≤18 years, the CBCL/6-18 will be used.

The same scale will be completed by the parent(s)/legal representative(s).

The CBCL/1½-5 comprises 100 questions and the CBCL/6-18 comprises 120 questions. In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

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

The CBCL/1½-5 will be grouped according to syndrome scales in Table 8-3 and the CBCL/6-18 will be grouped according to empirically based syndrome scales in Table 8-4.

**Change #35**

**Section 8.5 Palatability and ease of use questionnaires**

UCB has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg, taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

The number and percentage of subjects who respond to each of the categories presented for the following questionnaires will be summarized at each visit it is assessed:

- Tablet palatability and ease of use
- Oral solution palatability and ease of use

All palatability and ease of use questionnaire data will be listed.

**Has been changed to:**

UCB has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg, taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

The number and percentage of subjects who respond to each of the categories presented for the following questionnaires will be summarized at each visit it is assessed:

- Tablet palatability and ease of use
- Oral solution palatability and ease of use

Summaries will be performed overall and by seizure classification group (as defined in Section 3.2.12). All palatability and ease of use questionnaire data will be listed.

**Change #36**

**Section 8.4.10 Bayley-III assessment**

The Bayley-III assessments will be completed according to the tabular schedule of study procedures for subjects <18 months of age at study entry if enrolled in English-speaking countries.

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for this study.

The same scale will be completed at the Screening Visit (subjects enrolled directly into SP848),

Visit 1 (subjects enrolled from SP847 or other pediatric clinical studies in epilepsy), and Visit 13/Termination Visit (or ETV) (all subjects) for children from 1 month to <18 months of age enrolled in English-speaking countries.

**Has been changed to**

The Bayley-III assessments will be completed according to the tabular schedule of study procedures for subjects <18 months of age at study entry if enrolled in English-speaking countries.

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for this study.

The same scale will be completed for children from 1 month to <18 months of age enrolled in English-speaking countries.

**Change #37**

**Section 10 Efficacy Analysis**

The study efficacy variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, and quality of life assessments (PedsQL, health care resource use, and a LCM palatability and ease of use questionnaire).

All study efficacy variables will be summarized for the FAS, overall and repeated by efficacy seizure classification subgroup (where applicable), using the levels defined in Section 3.2.12. All summaries of efficacy data are descriptive; no statistical testing will be performed.

All efficacy variables will be listed.

**Has been changed to**

The study efficacy variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, and quality of life assessments (PedsQL and health care resource use).

All study efficacy variables will be summarized for the FAS, overall and repeated by efficacy seizure classification subgroup (where applicable), using the levels defined in Section 3.2.12. All summaries of efficacy data are descriptive; no statistical testing will be performed.

All efficacy variables will be listed.

**Change #38**

**Section 10.1 Seizure Counts**

At Screening of SP847 (or other LCM pediatric clinical studies in epilepsy) or at the Screening Visit of SP848 (for subjects who directly enrolled into SP848) subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous

4 weeks; this will serve as a historical Baseline. After the subject is enrolled in the SP848 study, seizure data will be collected in diaries provided to subjects/caregivers (including parents/legal guardians). Each subject/caregiver (including parent/legal guardian) will keep a diary to note daily seizure activity throughout the current study. The subject/caregiver (including parent/legal guardian) should be reminded to bring the diary with them at each clinic visit. The following information will be recorded:

- Seizure type
- Seizure frequency

Each seizure code in the clinical database will be mapped to exactly 1 of the ILAE seizure codes

based on the 1981 ILAE classification (Seizure Count CRF/eCRF module).

**Has been changed to:**

At Screening of SP847 (or other LCM pediatric clinical studies in epilepsy) or at the Screening Visit of SP848 (for subjects who directly enrolled into SP848) subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous

4 weeks; this will serve as a historical Baseline. After the subject is enrolled in the SP848 study, seizure data will be collected in diaries provided to subjects/caregivers (including parents/legal guardians). Each subject/caregiver (including parent/legal guardian) will keep a diary to note daily seizure activity throughout the current study. The subject/caregiver (including parent/legal guardian) should be reminded to bring the diary with them at each clinic visit. The following information will be recorded:

- Seizure type
- Seizure frequency

Each seizure code in the clinical database will be mapped to exactly 1 of the ILAE seizure codes based on the 1981 ILAE classification (Seizure Count CRF/eCRF module).

Determination of Baseline Period seizures will be made utilizing both the historical Baseline and the seizure diary data collected from the date of the Screening Visit to the day prior to the date of first dose of LCM.

**Change #39**

**Section 10.1.1 Seizure frequency per 28 days:**

For subjects with POS, seizure frequency per 28 days (as defined in Section 3.2.13) will be summarized descriptively and presented graphically at each visit and grouped by modal daily LCM dose (as defined in Section 3.2.8). Observed values will be summarized by visit and change from Baseline will be summarized for all post-Baseline visits, as appropriate.

**Has been changed to:**

For subjects with POS, seizure frequency per 28 days (as defined in Section 3.2.13) will be summarized descriptively and presented graphically at each visit and grouped by modal daily LCM dose (as defined in Section 3.2.8). Observed values will be summarized by visit and change from Baseline will be summarized for all post-Baseline visits, as appropriate.

Descriptive statistics will also be presented for the change from Baseline by modal daily LCM dose (as defined in Section 3.2.8) during the Titration Period, Post-Titration Period and the overall Treatment Period for the direct enrollers and the overall Treatment Period for rollover subjects and all subjects.

**Change #40**

**Section 10.1.2 Percent change from Baseline in 28-day seizure frequency**

For subjects with POS, descriptive statistics for percent change from Baseline (as defined in Section 3.2.14) in 28-day seizure frequency will be presented by seizure time intervals (as defined in Section 3.2.21) and modal daily LCM dose (as defined in Section 3.2.8). Any subject with seizure data during the time interval will be included in the summary for that seizure time interval.

Descriptive statistics will also be presented for percent change from Baseline in 28-day seizure frequency during the entire Treatment Period. Descriptive statistics for percent change from Baseline in 28-day seizure frequency during the Treatment Period will also be presented by Baseline seizure type (simple partial, complex partial, secondarily generalized). Only subjects

who experienced a seizure type during the Baseline Period will be included in the analysis for that seizure type with only the seizure frequencies of that seizure type being used in the analysis.

The percent change from Baseline in 28-day seizure frequency among completer cohorts (as defined in Section 3.2.19) will also be presented by modal daily LCM dose (as defined in Section 3.2.8).

**Has been changed to**

For subjects with POS, descriptive statistics for percent change from Baseline (as defined in Section 3.2.14) in 28-day seizure frequency will be presented by seizure time intervals (as defined in Section 3.2.21) and modal daily LCM dose (as defined in Section 3.2.8). Any subject with seizure data during the time interval will be included in the summary for that seizure time interval.

Descriptive statistics will also be presented for percent change from Baseline by modal daily LCM dose (as defined in Section 3.2.8) in 28-day seizure frequency during the Titration Period, Post-Titration Period and for the overall Treatment Period for direct enrollers and for the overall Treatment Period for the rollover subjects and all subjects. Descriptive statistics for percent change from Baseline in 28-day seizure frequency during the Treatment Period will also be presented by Baseline seizure type (simple partial, complex partial, secondarily generalized). Only subjects who experienced a seizure type during the Baseline Period will be included in the analysis for that seizure type with only the seizure frequencies of that seizure type being used in the analysis.

The percent change from Baseline in 28-day seizure frequency among completer cohorts (as defined in Section 3.2.19) will also be presented by modal daily LCM dose (as defined in Section 3.2.8).

**Change #41**

**Section 10.1.3 ≥50% response to treatment**

For subjects with POS, the number and percentage of ≥50% responders will be summarized by seizure time intervals and modal daily LCM dose (as defined in Section 3.2.8). This will also be presented separately by completer cohorts (as defined in Section 3.2.19), Responder status will be assessed as described in Section 3.2.15 for a given seizure time interval based on the seizure data recorded during that interval. The number and percentage of ≥50% responders will also be presented for the entire Treatment Period.

The number and percentage of ≥50% responders will be presented in the same manner as described above but presented separately by seizure type (simple partial, complex partial, secondarily generalized) and by seizure time intervals (as defined in Section 3.2.21).

**Has been changed to:**

For subjects with POS, the number and percentage with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders) will be summarized by seizure time intervals and modal daily LCM dose (as defined in Section 3.2.8). This will also be presented separately by completer cohorts (as defined in Section 3.2.19), Responder status will be assessed as described in Section 3.2.15 for a given seizure time interval based on the seizure data recorded during that

interval. The number and percentage of ≥50% responders will also be presented for the entire Treatment Period.

The number and percentage of ≥50% responders will be presented in the same manner as described above but presented separately by seizure type (simple partial, complex partial, secondarily generalized) and by seizure time intervals (as defined in Section 3.2.21).

**Change #42**

**Section 10.1.4 ≥75% response to treatment**

The analyses described in Section 10.1.3 for ≥50% response to treatment will also be performed for ≥75% response to treatment for subjects with POS.

**Has been changed to:**

The analyses described in Section 10.1.3 for ≥50% response to treatment will also be performed for subjects with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders).

**Change #43**

**Section 10.1.5 Seizure-free status**

The number and percentage of subjects achieving a seizure-free status (as defined in Section 3.2.18) will be presented by completer cohorts (as defined in Section 3.2.19) overall and by modal daily LCM dose (as defined in Section 3.2.8).

The number and percentage of subjects seizure-free among completer cohorts (as defined in Section 3.2.19) will also be presented separately by seizure type (simple partial, complex partial, secondarily generalized). Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21).

**Has been changed to**

The number and percentage of subjects achieving a seizure-free status (as defined in Section 3.2.18) will be presented by completer cohorts (as defined in Section 3.2.19) overall and by modal daily LCM dose and seizure classification subgroup (as defined in Sections 3.2.8 and 3.2.12).

The number and percentage of subjects seizure-free among completer cohorts (as defined in Section 3.2.19) will also be presented separately by seizure type (simple partial, complex partial, secondarily generalized). Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21).

**Change #44**

**Section 10.1.6 Seizure days per 28 days**

For subjects from SP0966 with generalized seizures, the number of seizure days per 28 days (as defined in Section 3.2.16) will be summarized descriptively and presented graphically at each visit and grouped by modal daily LCM dose (as defined in Section 3.2.8). Observed values will be summarized by visit.

**Has been changed to**

For subjects with generalized seizures, the number of seizure days per 28 days (as defined in Section 3.2.16) will be summarized descriptively and presented graphically at each visit and grouped by modal daily LCM dose (as defined in Section 3.2.8). Observed values will be summarized by visit.

**Change #45**

**Section 10.2.1 Clinical Global Impression of Change**

The Clinical Global Impression of Change is a 7-point categorical rating scale in which the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed according to the tabular schedule of study procedures.

The number and percentage of subjects by Clinical Global Impression of Change value will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of subjects with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of subjects with non-missing values.

Clinical Global Impression of Change data will be listed.

**Has been changed to**

The Clinical Global Impression of Change is a 7-point categorical rating scale in which the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed according to the tabular schedule of study procedures.

The number and percentage of subjects by Clinical Global Impression of Change value will be summarized by visit and Last Visit and grouped by modal daily LCM dose and Seizure Classification subgroup, using the levels defined in Sections 3.2.8 and 3.2.12. The denominator for the percentage calculation will be based on the number of subjects with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of subjects with non-missing values.

Clinical Global Impression of Change data will be listed.

**Change #46**

**Section 10.2.2 Caregiver Global Impression of Change**

The Caregiver Global Impression of Change is a 7-point categorical rating scale in which the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed according to the tabular schedule of study procedures.

The number and percentage of subjects by Caregiver Global Impression of Change value will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of subjects with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of subjects with non-missing values.

Caregiver Global Impression of Change data will be listed.

**Has been changed to**

The Caregiver Global Impression of Change is a 7-point categorical rating scale in which the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed according to the tabular schedule of study procedures.

The number and percentage of subjects by Caregiver Global Impression of Change value will be summarized by visit and Last Visit and grouped by modal daily LCM dose and Seizure Classification subgroup, using the levels defined in Sections 3.2.8 and 3.2.12. The denominator for the percentage calculation will be based on the number of subjects with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized by visit and Last Visit and grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. The denominator for the percentage calculation will be based on the number of subjects with non-missing values.

Caregiver Global Impression of Change data will be listed.

**Change #47**

**10.2.3 Pediatric Quality of Life Inventory (PedsQL)**

The multidimensional PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score and each of the 4 scale scores (defined in Section 3.2.22) will be summarized for each visit and for Last Visit. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8.

All PedsQL data will be listed.

**Has been changed to**

Calculated values and changes from Baseline for the total scale score and each of the 4 scale scores (defined in Section 3.2.22) will be summarized for each visit and for Last Visit. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8, and also by Seizure Classification subgroup, using the levels defined in Section 3.2.12. All changes from baseline will only be calculated for visits when the subject uses the same form of the questionnaire as administered at baseline.

All PedsQL data will be listed.

**Change #48**

**Section 10.2.4 Health care resource use**

For health care resource use parameters, the following will be evaluated: concomitant AEDs (as defined in Section 6.4.3), medical procedures, health care provider consultations not foreseen by the protocol, and hospitalization/ER visits. Health care resource use parameters will be collected according to the tabular schedule of study procedures.

**Has been changed to**

For health care resource use parameters, the following will be evaluated: concomitant medical procedures, health care provider consultations not foreseen by the protocol, and hospitalization/ER visits. Health care resource use parameters will be collected according to the tabular schedule of study procedures. Summaries will be performed overall and by Seizure Classification subgroup, using the levels defined in section 3.2.12.

**Changes #49-53**

**Section 10.2.3 Pediatric Quality of Life Inventory (PedsQL)**

**Section 10.2.4 Health care resource use**

**Section 10.2.4.1 Medical procedures**

**Section 10.2.4.2 Healthcare provider consultations**

**Section 10.2.4.3 Hospital stays and ER visits**

**Has been changed to**

**Section 10.3 Pediatric Quality of Life Inventory (PedsQL)**

**Section 10.4 Health care resource use**

**Section 10.4.1 Medical procedures**

**Section 10.4.2 Healthcare provider consultations**

**Section 10.4.3 Hospital stays and ER visits**

**Change #54**

**Section 10.2.5 Palatability and ease of use questions**

**Has been changed to:**

**Section 8.5 Palatability and ease of use questions**

**Change #55**

Added Table header Table 12-3 to Section 12.2 Other Significant TEAEs and removed (*) and footnote.

**Change #56**

Added section 12.3 AEs for PDILI

## 13.3 Amendment 3

Rationale for the amendment

The primary purpose of this amendment is for consistency with other SAPs and protocols in the LCM pediatric program and to incorporate comments from DRM2 review.

**Specific changes**

**Change #1**

SAP/Amendment Number and Date

Final SAP 27 Apr 2015

SAP – Amendment 1 18 Dec 2015

SAP – Amendment 2 8 Mar 2019

**Has been changed to:**

Final SAP 27 Apr 2015

SAP – Amendment 1 18 Dec 2015

SAP – Amendment 2 8 Mar 2019

SAP – Amendment 3 25 Nov 2019

**Change #2**

The wording of 'subjects' has changed to 'study participants' throughout the amended SAP text and TFL shells, to reflect the new UCB standard.

**Change #3**

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AE | adverse event |

| | |
|---|---|
| AED | antiepileptic drug |
| BMI | body mass index |
| BRIEF® | Behavior Rating Inventory of Executive Function® |
| BRIEF®-P | Behavior Rating Inventory of Executive Function® - Preschool Version |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CBCL | Child Behavior Checklist |
| CRF | Case Report Form |
| CV | coefficient of variance |
| DBP | diastolic blood pressure |
| DRM | Data Review Meeting |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| ER | emergency room |
| ETV | Early Termination Visit |
| FAS | Full Analysis Set |
| HRQoL | health-related quality of life |
| ILAE | International League Against Epilepsy |
| LCM | Lacosamide |
| MA | markedly abnormal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PDILI | Potential Drug Induced Liver Injury |
| PedsQL | Pediatric Quality of Life Inventory |
| PK | pharmacokinetic |
| PK-PPS | Pharmacokinetic Per-Protocol Set |

| | |
|---|---|
| PT | preferred term |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SOC | system organ class |
| SPD | Specification of Protocol Deviations |
| SS | Safety Set |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| ULN | upper limit of normal |
| VNS | vagus nerve stimulation |
| WHODD | World Health Organization Drug Dictionary |

**Has been changed to:**

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AE | adverse event |
| AED | antiepileptic drug |
| BMI | body mass index |
| BRIEF® | Behavior Rating Inventory of Executive Function® |
| BRIEF®-P | Behavior Rating Inventory of Executive Function® - Preschool Version |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CBCL | Child Behavior Checklist |
| CRF | Case Report Form |
| CV | coefficient of variance |

| | |
|---|---|
| DBP | diastolic blood pressure |
| DRM | Data Review Meeting |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| ER | emergency room |
| ETV | Early Termination Visit |
| FAS | Full Analysis Set |
| HRQoL | health-related quality of life |
| IIL | Initiating intravenous lacosamide Group |
| ILAE | International League Against Epilepsy |
| LCM | Lacosamide |
| MA | markedly abnormal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OLL | Open-label lacosamide Group |
| PDILI | Potential Drug Induced Liver Injury |
| PedsQL | Pediatric Quality of Life Inventory |
| PK | pharmacokinetic |
| PK-PPS | Pharmacokinetic Per-Protocol Set |
| PT | preferred term |
| RxL | Prescription lacosamide (eg, VIMPAT) Group |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SOC | system organ class |

| | |
|---|---|
| SPD | Specification of Protocol Deviations |
| SS | Safety Set |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| ULN | upper limit of normal |
| VNS | vagus nerve stimulation |
| WHODD | World Health Organization Drug Dictionary |

**Change #4**

**Section 2.3.1.2 Subjects enrolling directly into SP848**

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously received LCM will be permitted to enroll directly into SP848.

Beginning with Protocol Amendment 5.3 (specific to Japan), approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll at approximately 9 sites in Japan. Beginning with Protocol Amendment 5.4 (specific to China), approximately 60 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll in China.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control. Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator with the exception of subjects in Japan. For sites in Japan, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children or until the sponsor decides to discontinue the development of LCM in children in Japan.

The same study conditions described in Section 2.5.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

**Has been changed to:**

**Section 2.3.1.2 Study participants enrolling directly into SP848**

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously received LCM will be permitted to enroll directly into SP848.

Beginning with Protocol Amendment 5.3 (specific to Japan), approximately 46 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll at approximately 9 sites in Japan. Beginning with Protocol Amendment 5.4 (specific to China), approximately 60 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll in China.

Study participants who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible study participants will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control. Study participants will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator with the exception of study participants in Japan. For sites in Japan, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children or until the sponsor decides to discontinue the development of LCM in children in Japan. Original direct enrollers are study participants who directly enroll outside of Japan or China.

The same study conditions described in Section 2.5.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

Study participants may enroll in study EP0060 (intravenous therapy) of LCM without withdrawing from SP848. Study participants will continue to receive their SP848 assigned LCM daily dose during the iv trial. Ongoing adverse events and concomitant medications originating in the iv trials will be followed in SP848 until resolution.

**Change #5**

**Section 2.4 Determination of sample size**

Approximately 42 study participants from the SP847 study will be eligible to enroll in this open-label study. Approximately 200 other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. For sites in China, approximately 60 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly in to SP848. The purpose of enrolling these study participants directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for study participants ≥4 years of age.

**Has been changed to:**

Approximately 42 study participants from the SP847 study will be eligible to enroll in this open-label study. Approximately 200 other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. For sites in China, approximately 60 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly in to SP848. The purpose of enrolling these study participants directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for study participants ≥4 years of age. Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848.

**Change #6**

**Section 3.1 General presentation of summaries and analyses**

Approximately 42 subjects from the SP847 study will be eligible to enroll in this open-label study. Other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. For sites in China, approximately 60 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly in to SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

**Has been changed to:**

Approximately 42 study participants from the SP847 study will be eligible to enroll in this open-label study. Approximately 200 other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. For sites in China, approximately 60 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly in to SP848. The purpose of enrolling these study participants directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for study participants ≥4 years of age.

**Change #7**

**Section 3.1 General presentation of summaries and analyses**

Summaries for BRIEF-P will be presented overall for all applicable subjects and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥2 to <4 years
- ≥4 to <6 years

**Has been changed to:**

Summaries for BRIEF-P will be presented overall for all applicable study participants and additionally based on the subject's age at time of entry into study SP848, using the following age groups:

- ≥2 to <4 years

- ≥4 to <5 years

**Change #8**

**Section 3.2.9 Age and age at first diagnosis**

The age at first diagnosis will be given in years and will be derived applying all rules for missing date imputation (see Section 4.2.6) with the following formula:

(Date of first diagnosis of epilepsy – date of birth) / 365.25

**Has been changed to:**

Missing or partial epilepsy diagnosis date will be derived applying all rules for missing data imputation (see Section 4.2.6) and age at diagnosis will use the following formula, where applicable. The age at first diagnosis will be given in years:

If date of birth is a complete date then age at diagnosis will be calculated as:

(Date of first diagnosis of epilepsy – date of birth) / 365.25

If date of birth is a partial date then age at diagnosis will be calculated as:

(Enrollment age in years) – [(Informed consent date – Epilepsy diagnosis date) / 365.25]

If this produces a value negative then age at diagnosis will be set to zero.

**Change #9**

**Section 3.3 Definition of Baseline values**

In general, Baseline will be defined as the last non-missing value collected prior to the first dose of LCM for safety and efficacy variables unless otherwise noted for a specific type of data. The Baseline values from SP847 and other previous pediatric studies will be designated as Baseline values for SP848. The baseline value for seizure counts for directly enrolled subjects will be taken from the Historical Seizure Count CRF/eCRF module collected in SP848.

**Has been changed to:**

In general, Baseline will be defined as the last non-missing value collected prior to the first dose of LCM for safety and efficacy variables unless otherwise noted for a specific type of data. The Baseline value for seizure counts for directly enrolled study participants will be taken from the Historical Seizure Count CRF/eCRF module collected in SP848 in combination with the seizure diary data collected from the date of the Screening Visit to the day prior to the date of first dose of LCM.

For participants enrolling from EP0060 the baselines for the questionnaires will consider each EP0060 enrollment group separately, those are: IIL (not currently receiving LCM, i.e. LCM naïve), OLL (currently receiving oral LCM in open-label long term study), and RxL (currently receiving prescribed oral LCM from commercial supply, VIMPAT). For ILL group baseline will be Visit 1 from SP848, for OLL group baseline will come from SP848 using above baseline definition, and for RxL group there will be no baseline data as they were on oral LCM prior to EP0060.

**Change #10**

Added section 4.2.7 Missing data due to participation in solution for infusion formulation trials

Study participants who participated in the iv trial EP0060 while also enrolled in SP848 will have missing data for seizure frequency and drug dosing during the period of participation in the iv trial. As the duration of the iv trial is short, approximately 1 to 5 days, not imputation for data missing due to participation in the iv trial will be performed.

Study participants were assigned the same dose in EP0060 as that assigned in SP848 for the two weeks prior to the start of the iv trial. As such, time during the iv trial will not be subtracted from the exposure calculation (ie, exposure will be from the start of LCM treatment in SP848 trial until the date of last dose of LCM in SP848). The duration of treatment during EP0060 is approximately 1 to 5 days.

For the calculation of variables related to seizure frequency, the dates during participation in EP0060 will be considered as not done for the purpose of efficacy analyses for SP848 (ie, the dates will not be considered as days evaluated for seizure frequency). Due to the short nature of EP0060, only 1 to 5 days of seizure frequency data are expected to be missing due to participation in EP0060.

**Change #11**

**Section 5.1 Subject disposition**

The number of subjects screened (screened subjects include subjects who signed an ICF), in addition to the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure, will be presented. A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of subjects screened, number of subjects enrolled, and the number of subjects in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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

- The number of screened subjects
- The number and percentage of enrolled subjects
- The number and percentage of subjects in the SS
- The number and percentage of subjects in the PK-PPS
- The number and percentage of subjects in the FAS
- The number of subjects from each parent study
- The number of original direct enrollers
- The number of Japanese direct enrollers
- The number of Chinese direct enrollers

Additionally, a summary of disposition and discontinuation reasons will present the following for all subjects in the SS (overall and repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively), PK-PPS, and FAS:

- The number and percentage of subjects starting the study
- The number and percentage of subjects completing the study (defined as subjects who have 'Completed subject' selected as status at termination – see Study Termination eCRF module)
- The number and percentage of subjects completing 12, 24, 36 and >36 months of the study
- The overall number and percentage of subjects discontinuing and the number and percentage of subjects discontinuing by primary reason for discontinuation. If the subject discontinued the study and the Study Termination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of subjects enrolled under each protocol amendment (estimated by date of informed consent) will be presented for all global protocols, and separately, for Chinese direct enrollers from version 5.4 and for Japanese direct enrollers from version 5.3. This will also be presented in the subject data listings.

**Has been changed to:**

The number of study participants screened (screened study participants include study participants who signed an ICF), in addition to the number and percentage of those study participants who were screen failures, broken down by primary reason for screening failure, will be presented. A summary of disposition of study participants will be provided for all screened study participants. The date of first subject in (date of earliest entry visit for the SP848 study), date of last subject out (date of final scheduled or unscheduled visit), number of study participants screened, number of study participants enrolled, and the number of study participants in each analysis set (SS, PK-PPS, and FAS), will be summarized overall and by investigator site. Study participants who transferred sites will be summarized according to their original site.

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

- The number of screened study participants
- The number and percentage of enrolled study participants
- The number and percentage of study participants in the SS
- The number and percentage of study participants in the PK-PPS
- The number and percentage of study participants in the FAS
- The number of study participants from each parent study
- The number of original direct enrollers (excluding Japanese and Chinese direct enrollers)
- The number of Japanese direct enrollers
- The number of Chinese direct enrollers

Additionally, a summary of disposition and discontinuation reasons will present the following for all study participants in the SS (overall and repeated by weight band and seizure

classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively), PK-PPS, and FAS:

- The number and percentage of study participants starting the study
- The number and percentage of study participants completing the study (defined as study participants who have 'Completed subject' selected as status at termination – see Study Termination eCRF module)
- The number and percentage of study participants completing 12, 24, 36 and >36 months of the study
- The overall number and percentage of study participants discontinuing and the number and percentage of study participants discontinuing by primary reason for discontinuation. If the subject discontinued the study and the Study Termination eCRF module is not available, the reason for discontinuation will be reported as "UNKNOWN".

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

The number and percentage of study participants enrolled under each protocol amendment (estimated by date of informed consent) will be presented for all global protocols, and separately, for Chinese direct enrollers from version 5.4 and for Japanese direct enrollers from version 5.3. This will also be presented in the subject data listings.

**Change #12**

**Section 6.4.1 Number of previous AEDs**

The number of previous AEDs defined as AEDs taken and stopped >28 days prior to entry into the study, will be summarized for the SS based on the following categorization: 1-3 AEDs, 4-6 AEDs, and ≥7 AEDs. This summary will be based on the History of Previous AED Treatment CRF/eCRF module for applicable studies which only includes AEDs stopped prior to study entry. For subjects who rolled over from the SP0966 study, previous AEDs are defined as AEDs taken 12 months prior to informed consent date and stopped >28 days prior to entry into SP0966.

**Has been changed to:**

The number of previous AEDs defined as AEDs taken and stopped >28 days prior to entry into the study, will be summarized for the SS based on the following categorization: 0 AED, 1-3 AEDs, 4-6 AEDs, and ≥7 AEDs. This summary will be based on the History of Previous AED Treatment CRF/eCRF module for applicable studies which only includes AEDs stopped prior to study entry. For study participants who rolled over from the SP0966 study, previous AEDs are defined as AEDs taken 12 months prior to informed consent date and stopped>28 days prior to entry into SP0966.

**Change #13**

**Section 6.4.2 Concomitant AEDs taken at the start of the SP848 Treatment Period**

Concomitant AEDs taken at the start of the SP848 Treatment Period are defined as AEDs taken concomitantly with LCM at the time of first dose of LCM in SP848.

The number of concomitant AEDs taken at the start of the SP848 Treatment Period will be summarized for the SS based on the following categorization: 1 AED, 2 AEDs, and 3 AEDs. The number and percentage of subjects taking concomitant AEDs at the start of the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

**Has been changed to:**

Concomitant AEDs taken at the start of the SP848 Treatment Period are defined as AEDs taken concomitantly with LCM at the time of first dose of LCM in SP848.

The number of concomitant AEDs taken at the start of the SP848 Treatment Period will be summarized for the SS based on the following categorization: 0 AED, 1 AED, 2 AEDs, 3 AEDs and ≥4 AEDs. The number and percentage of study participants taking concomitant AEDs at the start of the SP848 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

**Change #14**

**Section 8.4.2 Electrocardiograms (ECGs)**

For ECGs, Baseline will be defined as the average of all pre-dose interpretable readings. For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

**Has been changed to:**

For ECGs, Baseline will be defined as the average of all pre-dose interpretable readings. Assessments with missing time on day of first dose will be assumed pre-dose. For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

**Change #15**

**Section 8.4.9 BRIEF-P and BRIEF assessment**

The BRIEF-P/BRIEF assessments will be completed according to the tabular schedule of study procedures, only in countries where a validated translated version is available.

The BRIEF-P and BRIEF are validated tools that will be used for the evaluation of subjects ≥2 to <6 years of age, and ≥5 to ≤18 years of age, respectively.

**Has been changed to:**

The BRIEF-P/BRIEF assessments will be completed according to the tabular schedule of study procedures, only in countries where a validated translated version is available.

The BRIEF-P and BRIEF are validated tools that will be used for the evaluation of study participants ≥2 to <5 years of age, and ≥5 to ≤18 years of age, respectively.

**Change #16**

**Section 8.5 Palatability and ease of use questionnaires**

UCB has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will

assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg, taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

The number and percentage of subjects who respond to each of the categories presented for the following questionnaires will be summarized at each visit it is assessed:

- Tablet palatability and ease of use
- Oral solution palatability and ease of use

Summaries will be performed overall and by seizure classification group (as defined in Section 3.2.12). All palatability and ease of use questionnaire data will be listed.

**Has been changed to:**

UCB has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg, taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

The number and percentage of study participants who respond to each of the categories presented for the following questionnaires will be summarized at each visit it is assessed:

- Tablet palatability and ease of use
- Oral solution palatability and ease of use

Summaries will be performed overall and by seizure classification group (as defined in Section 3.2.12), with percentages based on the number of study participants with non-missing responses for the specified visit. All palatability and ease of use questionnaire data will be listed.

## 13.4 Amendment 4

**Rationale for the amendment**

This amendment was done to reflect the changes in Protocol Amendment #8.

**Specific changes**

**Change #1**

SAP/Amendment Number and Date

Final SAP 27 Apr 2015

SAP – Amendment 1 18 Dec 2015

SAP – Amendment 2 8 Mar 2019

SAP – Amendment 3 25 Nov 2019

**Has been changed to:**

Final SAP 27 Apr 2015

SAP – Amendment 1 18 Dec 2015

SAP – Amendment 2 8 Mar 2019

SAP – Amendment 3 25 Nov 2019

SAP – Amendment 4 15 Jan 2020

**Change #2**

Added abbreviations for BCR and COVID-19.

**Change #3**

**2.1 Study objectives**

**2.1.1 Primary objective**

- To obtain information about the safety, tolerability, and pharmacokinetic (PK) of Lacosamide (LCM) during long-term exposure

**2.1.2 Secondary objective**

- To obtain preliminary efficacy data on seizure frequency during long-term exposure

**2.1.3 Other objectives**

- To allow study participants who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow study participants who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM

- Protocol Amendment 5.3 (specific to Japan) allows approximately 46 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM to directly enroll at approximately 9 sites in Japan
- Protocol Amendment 5.4 (specific to China) allows approximately 60 additional pediatric study participants with partial-onset seizures aged ≥4 years to ≤17 years who have not previously received LCM to directly enroll in China
- Protocol Amendment 6 allows approximately 75 additional eligible pediatric study participants with epilepsy who participated in EP0060 to continue to receive LCM

**Has been changed to:**

**2.1 Study objectives**

The objectives of this study are:

- To obtain information about the safety, tolerability, and pharmacokinetic (PK) of Lacosamide (LCM) during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long-term exposure
- To allow study participants who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow study participants who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM

**Change #4**

**2.2.1 Primary variables**

Safety, tolerability, and PK will be assessed using the following variables:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver, or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner Stage (if applicable)
- Plasma concentrations of LCM (for population PK analysis) and concomitant antiepileptic drugs (AEDs)

- Achenbach Child Behavior Checklist (CBCL) for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales for children <18 months of age at time of enrollment (applicable only to study participants enrolled in English-speaking countries)
- Cognitive function assessments (Behavior Rating Inventory of Executive Function – Preschool Version [BRIEF-P]/ Behavior Rating Inventory of Executive Function [BRIEF]) (if applicable)

**2.2.2 Secondary variables**

Efficacy will be assessed using the following variables:

- Seizure counts, which will be assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Quality of life assessments (Pediatric Quality of Life Inventory [PedsQL]) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)
- LCM palatability and ease of use questionnaire

**Has been changed to:**

**2.3 Safety variables**

**2.3.1 Primary safety variables**

The primary safety variables are as follows:

- Incidence of Treatment Emergent Adverse events (TEAEs)
- Incidence of Serious Adverse Events (SAEs)
- Subject withdrawal from the study due to TEAEs

**2.3.2 Other safety variables**

The other safety variables are:

- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner Stage (if applicable)
- Achenbach Child Behavior Checklist (CBCL) for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior

- Bayley-III scales for children <18 months of age at time of enrollment (applicable only to study participants enrolled in English-speaking countries)
- Cognitive function assessments (Behavior Rating Inventory of Executive Function – Preschool Version [BRIEF-P]/ Behavior Rating Inventory of Executive Function [BRIEF]) (if applicable)
- LCM palatability and ease of use questionnaire

### 2.3.3 Pharmacokinetic variables

#### 2.3.3.1 Primary Pharmacokinetic variables

No primary PK variables are defined for this study.

#### 2.3.3.2 Other Pharmacokinetic variables

The other PK variables are:

- Plasma concentration of LCM (for population PK analysis) and concomitant antiepileptic drugs (AEDs)

### 2.3.4 Efficacy variables

#### 2.3.4.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

#### 2.3.4.2 Secondary efficacy variables

The secondary efficacy variables, based on daily seizure diaries are:

- Percent change from Baseline in 28-day partial-onset seizure frequency
- ≥50% reduction in 28-day partial-onset seizure frequency
- ≥75% reduction in 28-day partial-onset seizure frequency
- Seizure days per 28 days (subjects with generalized seizures only)
- Seizure-free status

#### 2.3.4.3 Other efficacy variables

The other efficacy variables are:

- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Quality of life assessments (Pediatric Quality of Life Inventory [PedsQL$^{TM}$]) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)
- All seizure frequency analyses as described in secondary efficacy variables (presented for the overall Treatment Period only) may be additionally presented by modal daily dose group, by seizure type, by seizure classification subgroup, by time interval, by visit or time period, or by completer cohort.

**Change #5**

**2.4.1.1 Study participants enrolling directly into SP848**

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously received LCM will be permitted to enroll directly into SP848.

Beginning with Protocol Amendment 5.3 (specific to Japan), approximately 46 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll at approximately 9 sites in Japan. Beginning with Protocol Amendment 5.4 (specific to China), approximately 60 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll in China.

Study participants who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible study participants will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control. Study participants will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator with the exception of study participants in Japan. For sites in Japan, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children or until the sponsor decides to discontinue the development of LCM in children in Japan. Original direct enrollers are study participants who directly enroll outside of Japan or China.

The same study conditions described in Section 2.5.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

Study participants may enroll in study EP0060 (intravenous therapy) of LCM without withdrawing from SP848. Study participants will continue to receive their SP848 assigned LCM daily dose during the iv trial. Ongoing adverse events and concomitant medications originating in the iv trials will be followed in SP848 until resolution.

**Has been changed to:**

**2.3.1.2 Study participants enrolling directly into SP848**

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously received LCM will be permitted to enroll directly into SP848.

Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will be permitted to directly enroll at approximately 9 sites in Japan. Beginning with Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly enroll into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose

will be titrated to a level to optimize tolerability and seizure control. Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator.

SP848 includes subjects ≥1 month to ≤18 years of age since subjects who complete SP847 or another applicable LCM pediatric epilepsy study in subjects <18 years of age may have aged to 18 years old by the time they complete that study and enroll in SP848.

The same study conditions described in Section 2.5.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and LCM taper) also apply.

**Change #6**

**2.4 Determination of sample size**

Approximately 42 study participants from the SP847 study will be eligible to enroll in this open-label study. Approximately 200 other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. For sites in Japan, approximately 46 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly into SP848. For sites in China, approximately 60 additional eligible pediatric study participants ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will enroll directly in to SP848. The purpose of enrolling these study participants directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for study participants ≥4 years of age. Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848.

**Has been changed to:**

**2.5 Determination of sample size**

Approximately 42 study participants from the SP847 study will be eligible to enroll in this open-label study. Other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional

long-term safety data will be included in planned LCM marketing applications for study participants ≥4 years of age.

Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848. Protocol Amendment 8 allows an enrollment increase from 75 to 100 eligible pediatric subjects ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of subjects down to 1 month of age.

In total, up to approximately 400 subjects may be eligible to participate in SP848.

**Change #7**

**3.1 General presentation of summaries and analyses**

The age group for the age at time of entry into study SP848 is updated to following:

- ≥1 month to <4 years
- ≥4 to <18 years
- Total ≥1 month to <18 years
- ≥18 years
- All subjects

**Change #8**

**3.1 General presentation of summaries and analyses**

For summaries of PedsQL, the age group of ≥1 month to ≤12 months, >12 months to ≤24 months, and Total ≥5 years to ≤18 years was added in.

**Change #9**

**3.2.9 Age and age at first diagnosis**

Age at entry into SP848 will be given in years and will be derived applying all rules for missing date imputation (see Section 4.2.6) and the SDTM derivation definition, in the analysis dataset. The age at entry into the previous pediatric study is migrated from the previous pediatric study into the SP848 SDTM.

Missing or partial epilepsy diagnosis date will be derived applying all rules for missing data imputation (see Section 4.2.6) and age at diagnosis will use the following formula, where applicable. The age at first diagnosis will be given in years.

If date of birth is a complete date then age at diagnosis will be calculated as:

(Date of first diagnosis of epilepsy – date of birth) / 365.25

If date of birth is a partial date then age at diagnosis will be calculated as:

(Enrollment age in years) – [(Informed consent date – Epilepsy diagnosis date) / 365.25]

If this produces a value negative then age at diagnosis will be set to zero.

**Has been changed to:**

### 3.2.9 Age and age at first diagnosis

Age at entry into SP848 will be given in years. For direct enrollers and subjects with a complete date of birth available, age at entry into SP848 will use the SDTM derivation in the analysis dataset. For rollover subjects without a complete date of birth available, age at entry into SP848 will be calculated as:

Age at entry into the previous pediatric study + (number of calendar months between the informed consent dates of the previous pediatric study and SP848)/12.

The age at entry into the previous pediatric study is migrated from the previous pediatric study into the SP848 SDTM.

Missing or partial epilepsy diagnosis date will be derived applying all rules for missing data imputation (see Section 4.2.6) and age at diagnosis will use the following formula, where applicable. The age at first diagnosis will be given in years.

If date of birth is a complete date then age at diagnosis will be calculated as:

(Date of first diagnosis of epilepsy – date of birth) / 365.25

If date of birth is a partial date then age at diagnosis will be calculated as:

(Enrollment age in years) – [(Informed consent date – Epilepsy diagnosis date) / 365.25]

If this produces a value negative then age at diagnosis will be set to zero.

**Change #10**

### 3.2.22 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. The PedQL Measurement Model consists of developmentally appropriate forms for pediatric study participants ≥1 month to ≤12 months, ≥13 months to ≤24 months, >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. For each subject, the same version that is used at Baseline should be used for 12 months and thereafter the appropriate age versions should be used.

PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales:

- Physical Functioning
- Emotional Functioning
- Social Functioning
- School Functioning

The PedsQL assessment is retrospective to the prior one month, and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: never, almost never, sometimes, often, or almost always). These scores of 0 to 4 will be transformed by the function: 100 – (response x 25) in order to generate scores of 0, 25, 50, 75, and 100 where a higher value represents a better health-related quality of life (HRQoL).

Each scale score is then calculated as the mean of the non-missing categorized items if 50% or more of the items are non-missing.

The above algorithm will also be used to calculate an overall total scale score (all scales), and the psychosocial health summary score (a combination of the emotional, social and school functioning questions) for each subject.

**Has been changed to:**

**3.2.22 Pediatric Quality of Life Inventory (PedsQL)**

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≥1 month to ≤18 years of age. The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric study participants ≥1 month to ≤12 months, ≥13 months to ≤24 months, >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. For each subject, the same version that is used at Baseline should be used for 12 months and thereafter the appropriate age versions should be used.

For versions intended for subjects ≤24 months of age, PedsQL infant scale scores will be calculated for each of the following 5 PedsQL scales:

- Physical Functioning
- Physical Symptoms
- Emotional Functioning
- Social Functioning
- Cognitive Functioning

For versions intended for subjects >2 years of age, PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales:

- Physical Functioning
- Emotional Functioning
- Social Functioning
- School Functioning

For versions intended for subjects >8 years of age, Physical Functioning refers to questions [redacted]"; Emotional Functioning refers to questions [redacted]; Social Functioning refers to questions [redacted]; School Functioning refers to questions "[redacted].

The PedsQL assessment is retrospective to the prior one month, and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: never, almost never, sometimes, often, or almost always). These scores of 0 to 4 will be transformed by the function in order to generate scores of 0, 25, 50, 75, and 100 where a higher value represents a better health-related quality of life (HRQoL):

Item transform score = 100 – (item raw score x 25)

Each PedsQL scale or dimension score is then calculated as the mean of the transformed item scores from items of the considered dimension. In the case of item-level missing data, these will be replaced by the average of non-missing item scores from the considered dimension, if at least 50% of the items from that dimension are non-missing.

The above algorithm will also be used to calculate the PedsQL total score (all items), the psychosocial health summary score (a combination of the emotional, social and cognitive functioning items), and the physical health summary score (a combination of the physical functioning and physical symptoms items) for each subject ≤24 months of age. Also, the PedsQL total score (all items), the psychosocial health summary score (a combination of the emotional, social and school functioning items) and the physical health summary score (the physical functioning items) will be calculated for each subject >2 years of age. These summary scores will be missing if any of the scale scores contributing to their calculation is missing.

**Change #11**

**Section 3.3 Definition of Baseline values**

The first dose date for rollover subjects and direct enrollers is clarified.

**Change #12**

**Section 3.4 Protocol deviations**

The following text has been added in this section:

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (COVID-19) will be documented.

**Change #13**

**3.5.3 Full Analysis Set**

Abbreviation of FAS is added in.

**Change #14**

**3.9 Changes to protocol-defined analysis**

The section of 3.9.1 and 3.9.2 is deleted, as the efficacy variables and summarization by various sub-groups were added in protocol amendment 8. Further, the sub-section numbering of Section 3.9.3 was updated 3.9.1.

**Change #15**

**5.1 Subject disposition**

The number and percentage of subject completing the study by interval, following categories were added in: <12 months, ≥48 months.

**Change #16**

**5.1 Subject disposition**

The following text has been added in this section:

The number and percentages of subjects 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 subjects in the SS. This will also be presented in the subject data listings.

**Change #17**

**5.2 Protocol deviations.**

The statement "The number and percentage of study participants with no important protocol deviations will also be summarized for the SS" is deleted.

**Change #18**

**6.1 Demographics and other Baseline characteristics**

The clinicaltrail.gov categories of age (≤18 years and 19 - < 65 years) are added in.

**Change #19**

**6.1 Demographics and other Baseline characteristics**

The summarization weight (in kg) at the entry of SP848 study is clarified.

**Change #20**

**8.2 Adverse Events**

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.123.2.12, respectively. Additional tables will also be presented by time interval using the definition in Section 3.2.5. The number and percentage of study 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 30 days after last dose of LCM 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 pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of study participants with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of study participants with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, the overall summary will be presented for the Titration Period, Post-

Titration Period and Treatment Period for the direct enrollers and the Treatment Period for the rollover study participants.

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

- Incidence of TEAEs
- Incidence of TEAEs with onset during the Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Post-Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Treatment Period for direct enrollers
- Incidence of TEAEs for direct enrollers
- Incidence of TEAEs for rollover study participants
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of TEAEs by relationship to LCM
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs related to Potentially Drug Induced Liver Injury (PDILI)
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of non-serious TEAEs occurring in at least 5% of study participants by relationship to LCM
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will also be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively.

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will be presented for the time intervals (using the definition in Section 3.2.5) of: ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months, >12 to

≤ 15 months, >15 to ≤18 months, >18 to ≤21 months, >21 to ≤24 months, and >24 to ≤ 30 months, >30 to ≤36 months, >36 to ≤42 months, >42 to ≤48 months, >48 months:

- Incidence of all TEAEs with onset during the Treatment Period
- Incidence of all serious TEAEs with onset during the Treatment Period
- Incidence of all TEAEs leading to discontinuation with onset during the Treatment Period

Incidence of all other significant TEAEs with onset during the Treatment Period (defined in Appendix 12.2)

In addition, summaries for the incidence of TEAEs overall, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation, incidence of other significant TEAEs, and TEAEs related to PDILI will be repeated presenting the site and subject number of all those study participants experiencing each TEAE as well as in subject data listings.

**Has been changed to:**

**8.2 Adverse Events**

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively. Additional tables will also be presented by time interval using the definition in Section 3.2.5. The number and percentage of study 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 pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first SP848 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first SP848 dose of LCM, or whose intensity worsened on or after the date of first SP848 dose of LCM. AEs occurring within 30 days after last dose of LCM 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.

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent adverse events and treatment-emergent serious adverse events will be published.

All AEs reported during the study including pre-treatment and post-treatment AEs will be provided in a subject data listing.

An overview of the incidence of TEAEs will provide the overall summary of TEAEs and the numbers and percentages of study participants with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, the number and percentage of all deaths (if applicable), and the number and percentage of study participants with AEs leading to death (if applicable) will also be summarized. This overall summary will be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, the overall summary will be presented for the Titration Period, Post-Titration Period and Treatment Period for the direct enrollers and the Treatment Period for the rollover study participants.

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

- Incidence of TEAEs
- Incidence of TEAEs with onset during the Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Post-Titration Period for direct enrollers
- Incidence of TEAEs with onset during the Treatment Period for direct enrollers
- Incidence of TEAEs for direct enrollers
- Incidence of TEAEs for rollover study participants
- Incidence of serious AEs
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of TEAEs leading to discontinuation from the study
- Incidence of TEAEs by relationship to LCM
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs related to Potentially Drug Induced Liver Injury (PDILI) defined in Appendix 12.3 )
- Incidence of pediatric growth-, neurodevelopment-, behavior-, and endocrine-related TEAEs (defined in Appendix 12.4)
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of non-serious TEAEs occurring in at least 5% of study participants by relationship to LCM
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will also be repeated by weight band and seizure classification subgroup using the levels defined in Sections 3.2.10 and 3.2.12, respectively.

- Incidence of TEAEs
- Incidence of serious AEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation from the study
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of drug-related TEAEs by seriousness
- Incidence of other significant TEAEs (defined in Appendix 12.2).

The following summaries of AEs will be presented for the time intervals (using the definition in Section 3.2.5) of: ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months, >12 to ≤ 15 months, >15 to ≤18 months, >18 to ≤21 months, >21 to ≤24 months, and >24 to ≤ 30 months, >30 to ≤36 months, >36 to ≤42 months, >42 to ≤48 months, >48 months:

- Incidence of all TEAEs with onset during the Treatment Period
- Incidence of all serious AEs with onset during the Treatment Period
- Incidence of all serious TEAEs with onset during the Treatment Period
- Incidence of all TEAEs leading to discontinuation from the study with onset during the Treatment Period
- Incidence of all other significant TEAEs with onset during the Treatment Period (defined in Appendix 12.2)

In addition, summaries for the incidence of TEAEs overall, incidence of serious AEs, incidence of serious TEAEs, incidence of TEAEs leading to discontinuation from study, incidence of other significant TEAEs, TEAEs related to PDILI, and pediatric growth-, neurodevelopment-, behavior-, and endocrine-related TEAEs will be repeated presenting the site and subject number of all those study participants experiencing each TEAE as well as in subject data listings.

**Change #21**

**8.3 Clinical laboratory evaluations**

The abbreviations of AST, ALT and GGT were added in at first occurrence.

To determine the correct abnormality using age range, the age that would be considered at each visit/assessment is updated.

**Change #22**

**8.4.1 Vital signs, body weight, height and BMI**

The following statement is deleted:

Additionally, a subject will be considered to have marked bradycardia if the pulse rate is <45bpm and an AE mapped to the PT bradycardia is reported for the subject. A listing of vital signs data will be provided for all study participants with marked bradycardia.

**Change #23**

**8.4.1 Vital signs, body weight, height and BMI**

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

**Has been changed to:**

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

**Change #24**

**8.4.2 Electrocardiograms (ECG)**

To determine the correct abnormality using age range, the age that would be considered at each visit/assessment is updated.

**Change #25**

Section 8.4.8 Assessment of suicidality is updated to Section 8.4.7 Assessment of suicidality.

**Change #26**

The Section 8.4.7 Achenbach Child Behavior Checklist (CBCL) is updated to Section 8.4.8 Achenbach Child Behavior Checklist (CBCL).

**Change #27**

**8.4.8 Achenbach Child Behavior Checklist (CBCL)**

The following statement is added in: The occurrence of certain problems and behaviors (in the past 2 months for the CBCL/1½-5 version and in the past 6 months for the CBCL/6-18 version.

**Change #28**

**8.4.8 Achenbach Child Behavior Checklist (CBCL)**

Standardized T-scores are determined for each subject's raw syndrome and overall scores based on the subject's age and sex. Tables mapping each raw score to the appropriate T-score are provided in the CBCL Professional Manual and will be reproduced programmatically.

Calculated T-score values and change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Calculated T-score values and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

**Has been changed to:**

Standardized T-scores are determined for each subject's raw syndrome and overall scores based on the subject's age and sex. Tables mapping each raw score to the appropriate T-score are provided in the CBCL Professional Manual. Standardized T-scores determined from each subject's raw syndrome scale scores will be reproduced programmatically using the spreadsheets "c15group2-probscales18moto5yrs" and "cbcgroup2-probscales6to18".

Raw score and change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Raw score and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

The Calculated T-score will be listed along raw-score and change from baseline of raw score.

A decrease from baseline (change from baseline <0) in the CBCL syndrome raw score will indicate improvement in behavior, while an increase (change from baseline > 0) indicates worsening.

In addition, for both the CBCL/1½-5 syndrome and /6-18 syndrome, subject will be categorized according to the Calculated T-score as follows:

- T-score is < 65 = "Normal"
- T-score is ≥ 65 = "Borderline or Clinical range (BCR)"

Summaries of shifts from Baseline to each post-Baseline visits, and from Baseline to Last Visit will also be provided based on the CBCL calculated T-score categories of Normal and BCR. The descriptive summarizes of change from baseline and shift summaries will be presented only when corresponding baseline value is available.

**Change #30**

**8.4.9.1 BRIEF-P Scores**

Calculated T-score values and change from Baseline for the three index scores and GEC for the BRIEF-P questionnaire will be summarized for each visit, and Last Visit.

All BRIEF-P assessment data will be listed.

**Has been changed to:**

Standardized T-scores are determined from each subject's raw GEC, inhibitory self-control, flexibility, emergent metacognition, and component scores. Tables that map each raw score to the appropriate T-score are provided in the BRIEF-P Professional Manual. Standardized T-scores determined from each subject's raw GEC score, subscale scores and 5 individual component scores will be produced programmatically using the spreadsheet "briefp-tscores".

Raw score values and change from Baseline for the three index scores and GEC for the BRIEF-P questionnaire will be summarized for each visit, and Last Visit.

The Calculated T-score will be listed along raw score and change from baseline of raw score.

A decrease from baseline (change from baseline <0) in the BRIEF-P syndrome raw score will indicate improvement in behavior, while an increase (change from baseline > 0) indicates worsening.

In addition, for BRIEF-P, subject will be categorized according to the Calculated T-score as follows:

- T-score is < 65 = "Normal"
- T-score is ≥ 65 = "Elevated"

Summaries of shifts from Baseline to each post-Baseline visits, and from Baseline to Last Visit will also be provided based on BRIEF-P calculated T-score categories of Normal and Elevated.

The descriptive summarizes of change from baseline and shift summaries will be presented only when corresponding baseline value is available.

All BRIEF-P assessment data will be listed.

**Change #31**

**8.4.9.2 BRIEF Scores**

Calculated T-score values and change from Baseline for the two indexed scores (BRI and MI) and GEC for the BRIEF questionnaire will be summarized for each visit, and Last Visit.

All BRIEF assessment data will be listed.

**Has been changed to:**

Raw-score values and change from Baseline for the two indexed scores (BRI and MI) and GEC for the BRIEF questionnaire will be summarized for each visit, and Last Visit.

Standardized T-scores determined from each subject's raw GEC score, subscale scores and 5 individual component scores will be produced programmatically using the spreadsheet "brief-t-scores". The Standardized T-score will be listed along raw-score and change from baseline of raw score.

A decrease from baseline (change from baseline <0) in the BRIEF questionnaire raw score will indicate improvement, while an increase (change from baseline > 0) indicates worsening.

In addition, for BRIEF, subject will be categorized according to the Calculated T-score as follows:

- T-score is < 65 = "Normal"
- T-score is ≥ 65 = "Elevated"

Summaries of shifts from Baseline to each post-Baseline visits, and from Baseline to Last Visit will also be provided based on BRIEF calculated T-score categories of Normal and Elevated.

The descriptive summarizes of change from baseline and shift summaries will be presented only when corresponding baseline value is available.

All BRIEF assessment data will be listed.

**Change #32**

**9.1 Pharmacokinetic**

The summary of plasma concentration was updated to include timepoint.

**Change #33**

**10.4.1 Medical procedures**

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

Study participants who had any concomitant medical procedures during the course of the study based on the Concomitant Medical Procedures CRF/eCRF module will be listed. Additionally, study participants who had any procedures or surgeries prior to study entry based on the Procedure History CRF/eCRF module will also be listed.

**Has been changed to:**

### 8.4.11 Medical procedures

Subjects who had any concomitant medical procedures during the course of the study based on the Concomitant Medical Procedures eCRF module will be listed. Additionally, subjects who had any procedures or surgeries prior to study entry based on the Procedure History CRF/eCRF module will also be listed.

**Change #34**

The text "partial-onset" was added in heading of Section 10.1.2

**Change #35**

**10.1.3 ≥50% response to treatment**

For study participants with POS, the number and percentage with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders) will be summarized by seizure time intervals and modal daily LCM dose (as defined in Section 3.2.8). This will also be presented separately by completer cohorts (as defined in Section 3.2.19), Responder status will be assessed as described in Section 3.2.15 for a given seizure time interval based on the seizure data recorded during that interval. The number and percentage of ≥50% responders will also be presented for the entire Treatment Period.

The number and percentage of ≥50% responders will be presented in the same manner as described above but presented separately by seizure type (simple partial, complex partial, secondarily generalized) and by seizure time intervals (as defined in Section 3.2.21).

**Has been changed to:**

**10.1.3 ≥50% reduction in 28-days partial-onset seizure frequency**

For study participants with POS, the number and percentage with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders) will be summarized by seizure time intervals (as defined in Section 3.2.21) and by seizure type (simple partial, complex partial, secondarily generalized). Any subject with seizure data during the time interval will be included in the summary for that seizure time interval and by seizure type.≥75% reduction in 28-days partial-onset seizure frequency.).

**Change #36**

**10.1.4 ≥75% response to treatment**

The analyses described in Section 10.1.3 for ≥50% response to treatment will also be performed for study participants with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders).

**Has been changed to:**

**10.1.4 ≥75% reduction in 28-days partial-onset seizure frequency**

The analyses described in Section 10.1.3 for ≥50% reduction in 28-days partial-onset seizure frequency will also be performed for study participants with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders).

**Change #37**

**10.1.5 Seizure-free status**

The number and percentage of study participants achieving a seizure-free status (as defined in Section 3.2.18) will be presented by completer cohorts (as defined in Section 3.2.19) overall and by modal daily LCM dose and seizure classification subgroup (as defined in Sections 3.2.8 and 3.2.12).

The number and percentage of study participants seizure-free among completer cohorts (as defined in Section 3.2.19) will also be presented separately by seizure type (simple partial, complex partial, secondarily generalized). Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21).

**Has been changed to:**

**10.1.6 Seizure-free status**

The number and percentage of study participants achieving a seizure-free status (as defined in Section 3.2.18) will be presented for overall treatment period. This will be presented by completer cohorts (as defined in Section 3.2.19).

The number and percentage of study participants seizure-free among completer cohorts (as defined in Section 3.2.19) will also be presented separately by seizure type (simple partial, complex partial, secondarily generalized) for subjects with POS.

Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21). The number and percentage of study participants with seizure-free status at the end of each time interval during the treatment period will be presented separately by seizure type (simple partial, complex partial, secondarily generalized) for POS.

**Change #38**

**10.1.6 Seizure days per 28 days**

For study participants with generalized seizures, the number of seizure days per 28 days (as defined in Section 3.2.16) will be summarized descriptively and presented graphically at each visit and grouped by modal daily LCM dose (as defined in Section 3.2.8). Observed values will be summarized by visit.

**Has been changed to:**

**10.1.5 Seizure days per 28 days (subjects with generalized seizures only)**

For study participants with generalized seizures, the number of seizure days per 28 days (as defined in Section 3.2.16) will be summarized descriptively during the overall treatment period and grouped by modal daily LCM dose (as defined in Section 3.2.8).

**Change #39**

**Has been changed to:**

**10.3 Pediatric Quality of Life Inventory (PedsQL)**

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. The PedsQL will be completed up to two time per year and will be assessed according to the tabular schedule of study procedures. The Section 3.2.22 details how the scores for the core domains are calculated.

### 10.3.1 Pediatric Quality of Life Inventory Ages for ≤24 Months

The multidimensional PedsQL ≤24 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 5 scale scores will be summarized for each visit and for Last Visit. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8, and also by Seizure Classification subgroup, using the levels defined in Section 3.2.12. All changes from baseline will only be calculated for visits when the subject uses the same form of the questionnaire as administered at baseline.

All PedsQL ≤24 months data will be listed.

### 10.3.2 Pediatric Quality of Life Inventory Ages >2 years

The multidimensional PedsQL >2years generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 4 scale scores will be summarized for each visit and for Last Visit. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8, and also by Seizure Classification subgroup, using the levels defined in Section 3.2.12. All changes from baseline will only be calculated for visits when the subject uses the same form of the questionnaire as administered at baseline. All PedsQL >2 years data will be listed.

**Change #40**

Subsections of Section 10.4 were renumbers as Medical Procedures were moved to Section 10.4.1.

**Change #41**

**Section 12.3 Other Significant TEAEs**

The preferred terms are arranged alphabetically.

The preferred term “Cardiac arrest” is added in Table 12-3.

**Change #42**

**Section 12.3 List of AEs for Potentially Drug Induced Liver Injury (PDILI)**

MedDRA Preferred Terms “Alanine aminotransferase increased” and “Aspartate aminotransferase increased” have been added, duplicates have been removed, and Preferred Terms have been arranged in alphabetical order.

## STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

# Approval Signatures

**Name:** sp848-sap-amend-4

**Version:** 1.0

**Document Number:** CLIN-000164210

**Title:** SP0848: Draft SAP dated 04-Nov-2020

**Approved Date:** 18 Jan 2021

| Document Approvals | |
|---|---|
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 15-Jan-2021 19:28:55 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 18-Jan-2021 16:56:18 GMT+0000 |