STATISTICAL ANALYSIS PLAN

Study: EP0034

Product: Lacosamide

A MULTICENTER, OPEN-LABEL, LONG-TERM EXTENSION STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN PEDIATRIC SUBJECTS WITH EPILEPSY WITH PARTIAL-ONSET SEIZURES

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Confidentiality Statement

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	Alanine aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase
BMI	body mass index
BCR	borderline or clinical range
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
DBP	diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	electrocardiogram
eCRF	electronic Case Report Form
ER	emergency room
ETV	Early Termination Visit
FAS	Full Analysis Set
GGT	gamma-glutamyl transpeptidase
HRQoL	health-related quality of life
ILAE	International League Against Epilepsy
LCM	Lacosamide

LFT	liver function test
MA	markedly abnormal
MedDRA	Medical Dictionary for Regulatory Activities
PDILI	Potential Drug Induced Liver Injury
PedsQL	Pediatric Quality of Life Inventory
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
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 EP0034.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

- To assess the long-term safety and tolerability of Lacosamide (LCM) in pediatric subjects

2.1.2 Secondary objective

- To assess the efficacy of LCM during long-term exposure in pediatric subjects

2.1.3 Other objectives

- To assess behavior, cognition, quality of life, and development during long-term LCM exposure in pediatric subjects

2.2 Study variables

2.2.1 Primary Safety variables

The primary safety variables include the following:

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to study discontinuation

2.2.2 Other safety variables

The other safety variables include the following:

- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyl transferase [GGT]; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms (ECGs)
- Physical (Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations
- Vital signs (blood pressure and pulse rate)
- Body weight and height

- Change from Baseline in the Achenbach Child Behavior Checklist (CBCL) score: the Achenbach CBCL/1½-5 for children from 1.5 to 5 years of age and the Achenbach CBCL/6-18 for children ≥6 years of age
- Change from Baseline in the Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) score for subjects ≥2 and <5 years of age
- Change from Baseline in the Behavior Rating Inventory of Executive Function (BRIEF) score for subjects ≥5 years of age
- Change from Baseline in the Bayley-III scales in subjects <18 months of age at study entry (applicable only to subjects enrolled in English-speaking countries)

2.2.3 Efficacy variables

2.2.3.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

2.2.3.2 Secondary efficacy variables

The secondary efficacy variable planned for analysis will be based on seizure diary data from EP0034 and will include the following for all subjects:

- Percentage of seizure-free days during the study (presented for the overall Treatment Period only)

2.2.3.3 Other efficacy variables

The following other efficacy variables will be computed for subjects from SP0969:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving LCM in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)

- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL)
- Health care resource use: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays

2.3 Study design and conduct

This is a Phase 3, multicenter, open-label, extension study to obtain long-term safety and efficacy data in pediatric subjects with epilepsy with partial-onset seizures treated with LCM oral solution or LCM tablets as adjunctive therapy.

Subjects who have participated in SP0967 or SP0969, meet the eligibility requirements of this open-label extension study, and who consent or whose legal representative consents to participation can enroll into EP0034 for a maximum duration of approximately 2 years. The subject's eligibility for the study will be determined at Visit 1 (Week 0).

During the study, LCM will be available in either the oral solution formulation or tablet formulation. Subjects who are able and willing to swallow tablets may be dispensed LCM tablets during the Treatment Period, based on clinical judgment, regardless of their weight.

Approximately 500 subjects from SP0967 and SP0969 may be eligible to enroll in this open- label extension study. The number of sites is dependent on the number of enrolling centers from SP0967 and SP0969.

Treatment Period

After completion of the Transition Period in the previous pediatric study, subjects will have been transitioned to a dose of LCM according to their weight. Subjects will receive LCM 10mg/kg/day (oral solution) for subjects weighing <30kg, LCM 6mg/kg/day (oral solution) for subjects weighing ≥30kg to <50kg, and LCM 300mg/day (tablets) for subjects weighing ≥50kg during at least their first week in the Treatment Period of EP0034. After 1 week in EP0034, the investigator may adjust the LCM dose during the Treatment Period (see Table 7-1 in the protocol). Subjects may take either oral solution or tablets during the Treatment Period, based on clinical judgment, regardless of their weight.

Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction in each subject. LCM doses may be increased up to a maximum of LCM 600mg/day or 12mg/kg/day, whichever is lower based on body weight; LCM doses may be decreased to a minimum of LCM 100mg/day (tablet) or 2mg/kg/day (oral solution).

During the Treatment Period, study visits are scheduled at Weeks 0, 4, 8, 12, 20, 28, 36, 44, 52,

60, 72, 84, and 96. Telephone contacts are scheduled at Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56,

66, and 78.

At the completion of the study, investigators should discuss treatment options with the subject and/or their legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the last dose of LCM. The Safety Follow-Up Visit is not required for subjects

who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or legal representative) should taper LCM gradually. These subjects should complete Visit 13/Termination Visit and enter the Taper Period.

Subjects who prematurely discontinue the study should complete an Early Termination Visit (ETV). At the time of withdrawal from the study, investigators should discuss treatment options with the subject and/or their legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s). These subjects should complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the last dose of LCM.

Subjects who withdraw from the study prematurely and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or legal representative) should taper LCM gradually. These subjects should enter the Taper Period.

Taper Period

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

End of study and Safety Follow-up Period

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the last dose of LCM. A Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the last dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

Unscheduled visits may be conducted at the discretion of the investigator.

The maximum duration of LCM administration during EP0034 will be approximately 2 years.

Detailed tabular schedules of study procedures and a study schematic diagram are included in Sections 5.2 and 5.3 of the protocol, respectively.

2.4 Determination of sample size

Approximately 500 subjects from the SP0967 and the SP0969 study will be eligible to enroll in this open-label extension study. No formal hypothesis testing will be conducted in this study; therefore, no formal sample size calculations have been performed.

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 subjects in each category will be presented. The denominator for percentages will be based on the number of subjects 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 subjects (n), mean, standard deviation (SD), median, minimum, and maximum.

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

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

All summaries, unless otherwise stated below, will be presented overall for all subjects and additionally based on the subject's age at time of entry into study EP0034, using the following age groups:

- ≥1 month to <4 years
- ≥4 to <18 years

Summaries for PedsQL will be presented overall for all applicable subjects 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 subjects and additionally based on the subject's age at time of entry into study EP0034, 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 subjects and additionally based on the subject's age at time of entry into study EP0034, 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 subjects and additionally based on the subject's age at time of entry into study EP0034, using the following age groups:

- ≥2 to <4 years
- ≥4 to <5 years

Summaries for BRIEF will be presented overall for all applicable subjects and additionally based on the subject's age at time of entry into study EP0034, 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 subjects and additionally based on the subject's age at time of entry into study EP0034, 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 (eg, 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 EP0034 (ie, not the first dose of LCM from the previous study in which subjects participated prior to EP0034). 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 (eg, 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 EP0034 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.

3.2.3 Mapping of assessments performed at Early Termination Visit

Safety and efficacy assessments at an ETV that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the ETV if the assessment was scheduled to occur at that visit. 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 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.

3.2.4 Study visit labeling

Visits will be labeled in table summaries (according to the schedule outlined in Section 5.2 of the protocol) as follows:

- "Visit X, Week X" for scheduled visits during the Treatment Period

- "Taper Visit"
- "Safety Follow-up Visit"
- "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). The definition of 3-month intervals is based on the example durations in Table 3–1 which use 28-day months where the date of the first dose of LCM is Day 1:

Table 3–1: Definition of monthly interval durations during the first year

Interval	Duration Definition
Months 1 to 3	Days 1 to 84
Months 4 to 6	Days 85 to 168
Months 7 to 9	Days 169 to 252
Months 10 to 12	Days 253 to 336

Subsequent 3-month intervals are defined in a similar manner.

For the analysis of safety outcomes in the Treatment Period, a subject is included in the analysis for a 3-month interval if they are exposed to LCM at any time during that interval.

3.2.6 Last Visit

The Last Visit for all assessments in EP0034 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, 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.

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 EP0034.

The maximum daily LCM dose (mg/kg/day) is defined as the highest total daily dose a subject received during the Treatment Period in EP0034.

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 (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 subjects 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 parameters.

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 at entry and age at first diagnosis

Age at entry into EP0034 will be given in years. For subjects with complete date of birth available, age at entry in to EP0034 will use the SDTM derivation definition in the analysis dataset.

For subjects without a complete date of birth available, age at entry into EP0034 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 EP0034)/12.

The age at entry into the previous pediatric study and date of birth are migrated from the previous pediatric study into the EP0034 SDTM.

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

3.2.10 Weight band

Subjects will be classified as belonging to one of the following weight bands based on their weight at time of entry into study EP0034:

- <30kg
- ≥30 to <50kg
- ≥50kg

3.2.11 Body mass index (BMI)

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

$$BMI = \text{weight (kg)} / (\text{height [m]})^2$$

3.2.12 Enrollment groups

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

- SP0967
- SP0969

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.

If more than 1 cluster event occurred on the same day for Type II or Type III seizure, the seizure cluster 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 Type I seizure, the seizure clusters will be assigned to the correct seizure type and 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. $(SF_T - SF_B)$ is defined as the absolute reduction in 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). 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.

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 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 eCRF will not be counted as a seizure-free day.

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 has 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 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 a short-term iv substudy, days of participation in the substudy 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 subjects 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 subjects enrolled and treated with LCM for at least 6 months where a month is defined as 28 days.

Subjects 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

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 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

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

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 ≤4 years of age. The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric study 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 age 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 eCRF module) plus 1 day for hospital stays with a discharge date.

3.2.24 Age at time of visit/assessment

If date of birth is a complete date then age at the time of visit/assessment will be calculated as:

(Date of visit – date of birth)/365.25

If date of birth is a partial date then age at the time of visit/assessment will be calculated as:

(Enrollment age in years) + [(date of visit - informed consent date)/365.25]

This is converted to months by multiplying by 12 if required.

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 previous pediatric studies for efficacy and safety variables, unless otherwise noted for a specific type of data.

The Baseline value for seizure counts (only applicable for subjects from SP0969) will be taken from the subject diary completed during the 8-week Baseline Period before receiving LCM in study SP0969.

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 subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined separately in an important protocol deviations 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 subjects.

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 Evaluation Meetings (DEMs) and Data Cleaning meetings prior to database lock. A list of subjects with important protocol deviations will be agreed upon during the DEMs and will be documented in the DEM 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 subjects who took at least 1 dose of LCM in this long-term study. All safety analyses will be performed on the SS.

3.5.2 Full Analysis Set

The Full Analysis Set (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. Subjects whose efficacy data could not be source verified will be excluded from the FAS.

3.6 Treatment assignment and treatment groups

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

Where specified within this SAP, data will be summarized by age group (defined in Section 3.1).

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 SEP/2013). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

3.9.1 Examination of subgroups

A number of subgroups which were not protocol-defined have been included in Section 3.2.

3.9.2 Planned safety analyses

For planned safety analyses, the protocol states that:

Summary tables will be presented over the Treatment Period by 3-month periods and by categories of total duration of exposure.

However, only select AE tables will be presented by 3-month time intervals; incidence of all TEAEs with onset during the Treatment Period, incidence of all serious TEAEs with onset during the Treatment Period, incidence of drug-related TEAEs, incidence of TEAEs by maximum intensity, incidence of all TEAEs leading to discontinuation with onset during the Treatment Period, and incidence of all other significant TEAEs with onset during the Treatment Period.

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 antiepileptic drugs (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.

4.3 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 subjects

The FAS, defined in Section 3.5.2, 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

An overall summary of disposition will be provided for all screened subjects. All screened subjects is defined as all subjects enrolled into EP0034.

A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in (date of earliest Visit 1 for this study), date of last subject out (date of final scheduled or unscheduled visit), number of screened subjects, and the number of subjects in each analysis set (SS 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 subjects. The following will be summarized:

- The number and percentage of subjects in the SS
- 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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively) and FAS:

- The number and percentage of subjects starting the study
- The number and percentage of subjects completing the study
- The number and percentage of subjects completing <12 months, 12, and ≥24 months of the study, where 1 month is defined as 28 days
- 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. 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 important protocol deviations document, and additionally identified at the DEMs, will be listed. In addition, the number and percentage of subjects 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. The number and percentage of subjects with no important protocol deviations will also be summarized 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 study.

Demographic variables will be presented by weight band (using the levels defined in

Section 3.2.10), by enrollment group (using the levels defined in Section 3.2.12) and overall for the SS. The variables to be considered are:

- Age at entry into previous pediatric study (years) (as defined in Section 3.2.9)
- Age at entry into EP0034 (years) (as defined in Section 3.2.9) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years - <18 years)
- Gender
- Weight (kg)
- Weight (kg) at entry into EP0034
- Weight band at entry into EP0034 (as defined in Section 3.2.10)
- Height (cm)
- BMI (kg/m^2) (as defined in Section 3.2.11)
- Head circumference (cm)
- 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 subjects 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 subjects with concomitant diseases and conditions (medical history conditions noted as ongoing at study entry for the EP0034 study), except epilepsy, will be summarized by SOC and PT for the SS.

6.3 History of epilepsy

The history of epilepsy uses eCRF information collected at the time of entry into the previous pediatric LCM study.

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 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).

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.

6.3.3 Historical seizure counts

The Historical Seizure Counts 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.

6.4 Prior and concomitant medications

A listing of all medications taken during the study will be presented. Medications ongoing from the parent study will be migrated.

6.4.1 Concomitant AEDs taken at the start of the EP0034 Treatment Period

Concomitant AEDs taken at the start of the EP0034 Treatment Period are defined as AEDs taken concomitantly with LCM at the time of first dose of LCM in EP0034.

The number of concomitant AEDs taken at the start of the EP0034 Treatment Period will be summarized for the SS based on the following categorization: 0 AEDs, 1 AED, 2 AEDs, 3 AEDs, and 4 AEDs. The number and percentage of subjects taking concomitant AEDs at the start of the EP0034 Treatment Period will be summarized, separately, by WHODD chemical subgroup (level 4) and medication name, for the SS.

6.4.2 Concomitant AEDs taken during the EP0034 Treatment Period

Concomitant AEDs taken during the EP0034 Treatment Period are defined as AEDs taken concomitantly for at least one day in common with LCM in EP0034.

The number and percentage of subjects taking concomitant AEDs during the EP0034 Treatment Period will be summarized overall and, separately, by WHODD chemical subgroup (level 4) and medication name, for the SS.

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

6.4.3 Concomitant medications (excluding AEDs)

The number and percentage of subjects taking concomitant non-AEDs during the EP0034 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 on the SS.

8.1 Extent of exposure

All the summaries described below will also be presented 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 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.

8.2 Adverse events

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, select AE tables will also be presented by 3-month time intervals (as defined 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 EP0034 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first EP0034 dose of LCM, or whose intensity worsened on or after the date of first EP0034 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 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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12, respectively.

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

- Incidence of TEAEs
- 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 Section 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 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 enrollment group 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 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 3-month time intervals (as defined 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 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 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, 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 subjects 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 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 (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 ALT, AST, GGT, Total Bilirubin, and ALP.

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 EP0034 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 (as defined in Section 3.2.24).

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 schedules of study procedures.

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

Potential drug induced liver injury (PDILI) criteria as outlined in the protocol, will be checked at all laboratory assessments. The number and percentage of subjects meeting PDILI criteria (ie, ALT criteria and/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.

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

8.4.1 Vital signs, body weight, height, BMI, and head circumference

Vital signs (systolic BP [SBP], diastolic BP [DBP], and pulse rate) will be assessed after at least 3 minutes at rest in a supine position throughout the study, according to the tabular schedules of procedures. Body weight, height, and head circumference will also be assessed throughout the study, according to the tabular schedules of procedures.

Assessment of orthostatic changes (only in ambulatory subjects) will also be performed as follows: after the 3 minute measurement in supine position, the subject is asked to stand up, and SBP, DBP and pulse rate are taken approximately 1 minute and approximately 3 minutes after the subject stands up, as feasible.

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

Orthostatic changes of SBP, DBP, and pulse rate will be summarized for each visit 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 EP0034 LCM administration through to the end of the study. The age at the time of assessment will be used for determining MA (as defined in Section 3.2.24).

The number and percentage of subjects 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, and body weight are scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects 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 >180
	6m - <3y	<90 >150

Table 8–1: Vital signs abnormality criteria

Parameter	Age Range	Abnormality Criteria
	3y - <12y	<60 >130
	12y - <17y	≤50 >120
	≥17y	≤50 and a decrease from Baseline of ≥15 >120 and an increase from Baseline of >15
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120
	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤90 and a decrease from Baseline of ≥20 >180 and an increase from Baseline of >20
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	≤50 >105
	≥17y	≤50 and a decrease from Baseline of ≥15 >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 subjects with an AE mapped to the PT bradycardia or sinus bradycardia will be presented.

A subject data listing of all vital signs values including body weight, height, BMI, and head circumference for all subjects 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 schedules of 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. The age at the time of visit/assessment will be used for determining abnormality criteria (as defined in Section 3.2.24). 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

Parameter	Age Range	Abnormality Criteria
	≥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
	≥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.

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 schedules of 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 schedules of 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 schedules of procedures.

The complete neurological examination will include selected assessment of: general neurological status (level of consciousness, mental status, speech), cranial nerves, reflexes, motor system (general motor status, muscle strength, muscle tone), coordination/cerebellar function, and sensation.

Clinically significant neurological 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 schedules of procedures.

The brief neurological examination will include selected assessment of: general neurological status, reflexes, muscle strength, and coordination/cerebella 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 schedules of 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.

8.4.6 Tanner stage assessment

Tanner stage will be assessed throughout the study, according to the tabular schedules of 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 subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 1 [entry to study] or who will enter puberty during the course of the study).

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 schedules of study procedures.

For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All subjects who are ≥6 years of age will complete the Baseline/Screening version of the C-SSRS at entry to the study 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.

For subjects <6 years of age, the C-SSRS is not validated and will not be used. For those subjects, 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

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 subjects ≥6 years to ≤18 years, the CBCL/6-18 will be used.

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
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 appropriate scoring spreadsheets.

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 from the same questionnaire is available.

8.4.9 BRIEF-P and BRIEF assessment

The BRIEF-P/BRIEF assessments will be completed according to the tabular schedules 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 <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
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 appropriate scoring spreadsheets.

Raw scores 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 ≥ 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
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.

Raw scores 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 the appropriate scoring spreadsheets. 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 will indicate improvement in behavior, 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 schedules 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 should be completed for 1 year after the Baseline assessment of the previous study, even if the subject turns >18 months of age during that period.

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 scale scores entered on the eCRF module, and the change from Baseline for the scales, as well as the general adaptive composite sum scale score, will be summarized for each visit, and Last Visit.

All Bayley-III assessment data will be listed.

8.4.11 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.

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

9 EFFICACY ANALYSES

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 enrollment group (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.

9.1 Efficacy variables based on seizures

In general, efficacy variables based on seizures will be measured using data obtained from EP0034 subject diaries.

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 eCRF module).

9.1.1 Percentage of seizure-free days

The percentage of seizure-free days (as defined in Section 3.2.20) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will also be grouped by enrollment group. This will be repeated, separately by seizure type (simple partial, complex partial, or partial, secondary generalized).

9.1.2 Seizure frequency per 28 days

The following analyses will only be done for subjects who participated in SP0969.

Seizure frequency per 28 days (as defined in Section 3.2.13) will be summarized descriptively and presented graphically.

9.1.3 ≥50% reduction in 28-days partial-onset seizure frequency

The following analyses will only be done for subjects who participated in SP0969.

The number and percentage of subjects with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders as defined in Section 3.2.15) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will be repeated, separately by seizure type (simple partial, complex partial, or partial, secondary 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.

9.1.4 ≥75% reduction in 28-days partial-onset seizure frequency

The analyses described in Section 9.1.3 for percentage of subjects with ≥50% reduction in 28-days partial-onset seizure frequency will also be performed for study subjects with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders) for subjects who participated in SP0969.

9.1.5 Absolute and percent reduction in total partial-onset seizures

The following analyses will only be done for subjects who participated in SP0969.

Absolute and percent reduction from Baseline (as defined in Section 3.2.14) in total partial-onset seizures will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will be repeated, separately by seizure type (simple partial, complex partial, or partial, secondary generalized).

9.1.6 Seizure-free status

The number and percentage of subjects who achieved seizure-free status (as defined in

Section 3.2.18) will be summarized for the entire Treatment Period. This will be presented by completer cohorts (as defined in Section 3.2.19) and repeated by enrollment groups.

The number and percentage of study 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, or partial, secondary generalized).

Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21) and repeated by enrollment groups. The number and percentage of study subjects 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, partial, secondary generalized).

9.2 Analysis of other efficacy variables

The following other efficacy variables will be computed for all subjects in this study and summarized for the FAS.

9.2.1 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 subjects by Clinical Global Impression of Change value will be summarized by visit and Last Visit. This will be repeated by enrollment group. 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. 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.

9.2.2 Caregiver's Global Impression of Change

The Caregiver's 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 subjects by Caregiver's Global Impression of Change value will be summarized by visit and Last Visit. This will be repeated by enrollment group. 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. The denominator for the percentage calculation will be based on the number of subjects with non- missing values.

Caregiver's Global Impression of Change data will be listed.

9.2.3 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.

9.2.3.1 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. This will be repeated by enrollment group. 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.

9.2.3.2 Pediatric Quality of Life Inventory Ages >2 years

The multidimensional PedsQL >2 years 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. This will be repeated by enrollment group. For subjects 5 years and older at Baseline, changes from Baseline will be calculated for all visits, even when the questionnaire version used is different from the one at Baseline. For subjects less than 5 years at baseline, the change from Baseline will be calculated only when the same questionnaire version is used at Baseline and post-Baseline. All PedsQL >2 years data will be listed.

9.2.4 Health care resource use

For health care resource use parameters, the following will be evaluated: concomitant medications (see Section 6.4), 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 schedules of study procedures.

9.2.4.1 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.

9.2.4.2 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 subjects 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 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 subjects 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. Subjects 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.

10 PHARMACOKINETICS AND PHARMACODYNAMICS

This section is not applicable for this study.

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 >45	%	≤27 >45
	2y - <17y	%	≤29 >47	%	≤29 >47
	≥17y	%	≤85% of LLN ≥115% of ULN	%	≤85% of LLN ≥115% of ULN
Hemoglobin	<2y	g/dL	≤9.0	g/L	≤90
	2y - <17y	g/dL	≤9.5	g/L	≤95
	≥17y	g/dL	≤85% of LLN	g/L	≤85% of LLN
WBC/ Leukocytes	All	10^9/L	≤3.0 >16.0	G/L	≤3.0 >16.0
Lymphocytes Absolute	<2y	10^9/L	<1.0 >9.8	G/L	<1.0 >9.8
	2y - <6y	10^9/L	<0.7 >6.9	G/L	<0.7 >6.9
	≥6y	10^9/L	<0.6 >5.0	G/L	<0.6 >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 >600	G/L	≤100 ≥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 ≥5.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN	U/L	≥3.0 x ULN ≥5.0 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 >11.9	g/L	<30 >119
	1y - <17y	g/dL	<4.3 >12.0	g/L	<43 >120
	≥17y	g/dL	<4.3 >13.0	g/L	<43 >130
Albumin	<1y	g/dL	<1.6 >7.2	g/L	<16 >72
	≥1y - <17y	g/dL	<2.4 >8.4	g/L	<24 >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

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 >38	mmol/L	<15 >38
	≥17y	mEq/L	<18 >38	mmol/L	<18 >38
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <17y	mg/dL	<7.4 >11.7	mmol/L	<1.85 >2.925
	≥17y	mg/dL	≤7.6 ≥11.0	mmol/L	≤1.9 ≥2.75
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	1y - <17y	mg/dL	<1.8 >7.4	mmol/L	<0.5814 >2.3902
	≥17y	mg/dL	≤2.0 ≥6.0	mmol/L	≤0.646 ≥1.938
Potassium	<1y	mEq/L	≤3.0 ≥6.5	mmol/L	≤3.0 ≥6.5
	≥1y	mEq/L	≤3.0 ≥6.0	mmol/L	≤3.0 ≥6.0

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151
Glucose	>1m - <17y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99
	≥17y	mg/dL	<50 ≥200	mmol/L	<2.775 ≥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	>750	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 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y	ug/dL	≤3.8 ≥13.5	nmol/L	≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >4.5	g/L	<10 >45
	≥1y	g/dL	<1.2 >5.3	g/L	<12 >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 (subjects <12): Cr Cl ml/min=[Height (cm) * 0.55] / serum creatinine

[b] Cockroft equation (subjects >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 AEs

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
Brugada syndrome
Cardiac arrest
Cardiac fibrillation
Cardiac flutter
Cardiac pacemaker insertion
Conduction disorder
Defect conduction intraventricular
Electrocardiogram QT prolonged
Heart Rate decreased
Implantable defibrillator insertion

Table 12–3: Other significant TEAEs

MedDRA Preferred Term
Sick sinus syndrome
Sinus arrest
Sinus bradycardia
Torsade de pointes
Ventricular asystole
Ventricular fibrillation
Ventricular flutter
Ventricular tachyarrhythmia
Ventricular tachycardia
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Intentional overdose
Intentional self-injury
Multiple drug overdose intentional
Poisoning deliberate
Self injurious behaviour
Self-injurious ideation
Suicidal behaviour
Suicidal ideation
Suicide attempt
ADDITIONAL TERMS
Abnormal behaviour

Table 12–3: Other significant TEAEs

MedDRA Preferred Term
Appetite disorder
Decreased appetite
Diet refusal
Food aversion
Hypophagia
Loss of consciousness
Syncope

12.3 List of 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
Drug-induced liver injury
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic failure
Hepatic infiltration eosinophilic
Hepatic necrosis
Hepatic steatosis
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatotoxicity
Hyperbilirubinaemia
Icterus index increased
Jaundice
Jaundice cholestatic

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

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 28 May 2015

Has been changed to:

SAP – Amendment 1 10 Feb 2016

Change #2

Section 2.3 Study design and conduct

Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction in each subject. LCM doses may be increased up to a maximum of LCM 600mg/day or 12mg/kg/day, whichever is lower based on body weight.

Has been changed to:

Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction in each subject. LCM doses may be increased up to a maximum of LCM 600mg/day or 12mg/kg/day, whichever is lower based on body weight; LCM doses may be decreased to a minimum of LCM 100mg/day (tablet) or 2mg/kg/day (oral solution).

Change #3

Section 3.2.4 Study visit labeling

Visits will be labeled in table summaries (according to the schedule outlined in Section 5.2 of the protocol) as follows:

- "Visit X, Week X (Descriptor)" for scheduled visits during the Treatment Period
- "Taper Visit"
- "Safety Follow-up Visit"

- "Last Visit" (see below in Section 3.2.6 for further information)

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 5.2 of the protocol) as follows:

- "Visit X, Week X" for scheduled visits during the Treatment Period
- "Taper Visit"
- "Safety Follow-up Visit"
- "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

For the analysis of safety outcomes in the Treatment Period, a subject is included in the analysis for a 3-month interval if they are exposed to LCM for the duration of that interval.

Has been changed to:

For the analysis of safety outcomes in the Treatment Period, a subject is included in the analysis for a 3-month interval if they are exposed to LCM at any time during that 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 has 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 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 has 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 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 a short-term iv substudy, days of participation in the substudy will also not be considered in the assessment of seizure-free status.

Change #6

Section 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.

Has been changed to:

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

Change #7

Added the following section:

Section 3.9.5 Planned safety analyses

For planned safety analyses, the protocol states that:

Summary tables will be presented over the Treatment Period by 3-month periods and by categories of total duration of exposure.

However, only select AE tables will be presented by 3-month time intervals; 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, and incidence of all other significant TEAEs with onset during the Treatment Period.

Change #8

Section 5.1 Subject disposition

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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively) and FAS:

- The number and percentage of subjects starting the study
- The number and percentage of subjects completing the study
- The number and percentage of subjects completing <12 months and ≥12 months of the study, where 1 month is defined as 28 days
- 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”.

Has been changed to:

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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively) and FAS:

- The number and percentage of subjects starting the study
- The number and percentage of subjects completing the study
- The number and percentage of subjects completing <12 months and ≥12 months of the study, where 1 month is defined as 28 days
- 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".

Change #9

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 entry into the previous study will be summarized for the SS based on the International League Against Epilepsy (ILAE) Seizure Classification History eCRF module.

A subject will be classified as having a history of partial-onset seizures 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.

Has been changed to:

The number and percentage of subjects experiencing partial-onset seizures (type I), simple partial (type IA), complex partial (type IB), partial, secondary generalized seizures (type IC), generalized seizures (type II), absence (IIA1), atypical absence (IIA2), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), and atonic (IIF) seizures at any time prior to entry into the previous study will be summarized for the SS based on the International League Against Epilepsy (ILAE) Seizure Classification History eCRF module.

A subject will be classified as having a history of partial-onset seizures 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 generalized seizures (II) if the subject has a history of absence (IIA1), atypical absence (IIA2), 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 #10

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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, all AE summaries will be presented by 3-month time intervals (as defined 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.

Has been changed to:

AEs will be tabulated by MedDRA SOC and MedDRA PT; select tables will also be presented by weight band and enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, select AE tables will also be presented by 3-month time intervals (as defined 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.

And the following has been added:

The following summaries of AEs will be presented for the 3-month time intervals (as defined 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)

Change #11

Section 8.3 Clinical laboratory evaluations

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.

Has been changed to:

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.

Change #12

Section 8.4.2 Electrocardiograms (ECGs)

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.

Has been changed to:

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.

Change #13

Section 8.4.9 BRIEF-P and BRIEF assessment

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

Scale/Index	Questions
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
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 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.

13.2 Amendment 2

Rationale for the amendment

The primary purpose of this substantial amendment is for consistency with CTP amendment 2 dated 24th March 2017.

Specific changes

Change #1

SAP/Amendment Number and Date

SAP – Amendment 1 10 Feb 2016

Has been changed to:

SAP – Amendment 2 21 Mar 2019

Change #2

Section 2.2.3.1 Other efficacy variables

The following other efficacy variables will be computed for subjects from SP0969:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial- onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving LCM in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline

The following other efficacy variables will be computed for all subjects in EP0034:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) for subjects ≥2 years of age

- Health care resource use: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays

Was changed to:

The following other efficacy variables will be computed for subjects from SP0969:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial- onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving LCM in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL)
- Health care resource use: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays

Change #3

Section 2.3 Study design and conduct

The Taper Period (up to 6 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved:

LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper. A Taper Visit must be completed at the end of the Taper Period.

Was changed to:

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper. A Taper Visit must be completed at the end of the Taper Period.

Change #4

Section 3.1

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

- >2 to ≤4 years
- ≥5 to ≤7 years
- ≥8 to ≤12 years
- ≥13 to ≤18 years

Has been changed to:

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

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

- ≥13 to ≤18 years

Change #5

Section 3.2.22

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 for each subject.

Was changed to:

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 #6

The following paragraph was added to section 3.2.3

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 ETV will be assigned to the next scheduled visit, for which the corresponding assessment is scheduled following the last documented visit.

Change #7

Section 3.2.9 Age and age at first diagnosis

Was changed to:

Section 3.2.9 Age at entry and age at first diagnosis

Change #8

Section 3.2.13 Seizure frequency

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.

Was changed to:

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 Type II or Type III seizure, the seizure cluster 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 Type I seizure, the seizure clusters will be assigned to the correct seizure type and 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 #9

The following paragraph was added to section 3.2.22

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 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 age 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

Change #10

Section 3.4 Protocol deviations

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

Was changed to:

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

Change #11

Section 3.5.2 Full Analysis Set

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.

Was 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. Subjects whose efficacy data could not be source verified will be excluded from the FAS.

Change #12

Section 3.9.5 Planned safety analyses

However, only select AE tables will be presented by 3-month time intervals; incidence of all TEAEs with onset during the Treatment Period, incidence of all TEAEs leading to discontinuation with onset during the Treatment Period, and incidence of all other significant TEAEs with onset during the Treatment Period.

Was changed to:

However, only select AE tables will be presented by 3-month time intervals; incidence of all TEAEs with onset during the Treatment Period, incidence of all serious TEAEs with onset during the Treatment Period, incidence of drug-related TEAEs, incidence of TEAEs by maximum intensity, incidence of all TEAEs leading to discontinuation with onset during the Treatment Period, and incidence of all other significant TEAEs with onset during the Treatment Period.

Change #13

Section 4.2.2 Incomplete dates for Adverse events

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 28 days after last intake of LCM.

However, if the study termination year and year for the date which is 28 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.

Was changed to:

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.

Change #14

Section 5.1 Subject disposition

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

Was changed to:

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

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

Change #15

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), partial, secondary generalized seizures (type IC), generalized seizures (type II), absence (IIA1), atypical absence (IIA2), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), and atonic (IIF) seizures at any time prior to entry into the previous study will be summarized for the SS based on the International League Against Epilepsy (ILAE) Seizure Classification History eCRF module.

A subject will be classified as having a history of partial-onset seizures 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 generalized seizures (II) if the subject has a history of absence (IIA1), atypical absence (IIA2), 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).

Was 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 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 #16

The following text was added to section 6.4 Prior and concomitant medications

Medications ongoing from the parent study will be migrated.

Change #17

Section 6.4.1 Concomitant AEDs taken at the start of the EP0034 Treatment Period

The number of concomitant AEDs taken at the start of the EP0034 Treatment Period will be summarized for the SS based on the following categorization: 1 AEDs, 2 AEDs and 3 AEDs. The number and percentage of subjects taking concomitant AEDs at the start of the EP0034 Treatment Period will be summarized, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

Was changed to:

The number of concomitant AEDs taken at the start of the EP0034 Treatment Period will be summarized for the SS based on the following categorization: 1 AEDs, 2 AEDs, 3 AEDs, and > 3 AEDs. The number and percentage of subjects taking concomitant AEDs at the start of the EP0034 Treatment Period will be summarized, separately, by WHODD chemical subgroup (level 4) and preferred drug name, for the SS.

Change #18

Section 8.2

- 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.

Has been changed to:

- Incidence of 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 #19

Section 8.2 Adverse events

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)

Was changed to:

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 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)

Change #20

The following paragraph was added to section 8.3

Potential drug induced liver injury (PDILI) criteria as outlined in the protocol, will be checked at all laboratory assessments. The number and percentage of subjects meeting PDILI criteria (ie, ALT criteria and/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 #21

Section 6.2 Medical History and concomitant diseases

The number and percentage of subjects with a medical history condition (except epilepsy), at the time of entry into the previous pediatric study, 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.

Was changed to:

6.2 Medical History and Concomitant Diseases

6.2.1 Medical History

The number and percentage of subjects 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 subjects with concomitant diseases and conditions (medical history conditions noted as ongoing at study entry for the EP0034 study), except epilepsy, will be summarized by SOC and PT for the SS.

Change #22

Section 8.4.7, Emotionally reactive domain for CBCL/1½-5

Table 8–3: CBCL/1½-5

Syndrome scale	**Questions**
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
Attention problems	5, 6, 56, 59, 95
Emotionally reactive	21, 46, 51, 79, 28, 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,

Was changed to:

Table 8–3: CBCL/1½-5

Syndrome scale	**Questions**
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
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,

Change #23

Section 8.49.2

Table 8–6: BRIEF questionnaire scoring

Scale/Index	**Questions**
Working Memory	2, 9, 17, 19, 24, 27, 32, 33, 37, 57
Plan/Organize	11, 15, 18, 22, 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**

Was changed to:

Table 8–6: BRIEF questionnaire scoring

Scale/Index	**Questions**
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**

Change #24

Section 9.1.3

Section 9.1.3 Percentage of 50% responders

The number and percentage of ≥50% responders as defined in Section 3.2.15) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. 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. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. This will be repeated, separately, by 6-month completer cohorts (as defined in Section 3.2.19) and by seizure type (simple partial, complex partial, or secondarily generalized).

Was changed to:

Section 9.1.3 Percentage of subjects with ≥50% response to treatment

The number and percentage of subjects with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders as defined in Section 3.2.15) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. 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. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. This will be repeated, separately, by 6-month completer cohorts (as defined in Section 3.2.19) and by seizure type (simple partial, complex partial, or secondarily generalized).

Change #25

Section 9.1.4 Percentage of 75% responders

The analyses described in Section 9.1.3 for percentage ≥50% responders will also be performed for percentage of ≥75% responders for subjects who participated in SP0969.

Was changed to:

Section 9.1.4 Percentage of subjects with ≥75% response to treatment

The analyses described in Section 9.1.3 for percentage of subjects with ≥50% response to treatment will also be performed for percentage of subjects with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders) for subjects who participated in SP0969.

Change #26

Section 9.1.6 Percentage of subjects who achieved "seizure-free" status

Was changed to:

Section 9.1.6 Percentage of subjects who achieved Seizure-free status

Change #27

Section 9.2.3 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 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.

Was 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. All changes from Baseline will only be calculated for visits when the subject uses the same form of the questionnaire as administered at baseline.

Change #28

Section 12.2 Other significant AEs

The following MedDRA PTs are defined as other significant TEAEs.

MedDRA Preferred Term
HEPATOTOXICITY RELATED TERMS
Hepatitis toxic
Hepatotoxicity
CARDIAC AND ECG RELATED TERMS
Atrioventricular block complete

Atrioventricular block second degree
Bradyarrhythmia*
Bradycardia*
Cardiac pacemaker insertion
Atrial fibrillation
Atrial flutter
Sinus bradycardia*
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased*
Sick sinus syndrome
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation
Suicide attempt
Intentional self-injury
Self injurious behaviour
Self-injurious ideation
Intentional overdose
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope

*All cases with reported reduced heart rate will be reviewed and only cases with marked bradycardia (marked reduction in heart rate) with HR <45 bpm will be listed as 'Other Significant TEAEs'.

Has been changed to:

12.2 List of Other Significant AEs

MedDRA Preferred Term
CARDIAC AND ECG RELATED TERMS
Atrioventricular block third degree
Atrioventricular block second degree
Bradyarrhythmia
Bradycardia
Cardiac pacemaker insertion
Atrial fibrillation
Atrial flutter
Sinus bradycardia
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased
Sick sinus syndrome
Atrial conduction time prolongation
Atrioventricular dissociation
Conduction disorder
Cardiac fibrillation

Cardiac flutter
Sinus arrest
Torsade de pointes
Ventricular asystole
Ventricular flutter
Ventricular tachyarrhythmia
Implantable defibrillator insertion
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation
Suicide attempt
Intentional self-injury
Self injurious behaviour
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder
Decreased appetite
Diet refusal

Hypophagia
Food aversion
Abnormal behaviour

Change #29

A new appendix 12.3 has been added

13.3 Amendment 3

Rationale for the amendment

The primary purpose of this substantial amendment is to reflect the changes in Protocol amendment #3 and for consistency with other SAPs in the LCM pediatric program.

Specific changes

Change #1

SAP/Amendment Number	Date
SAP – Amendment 2	21 Mar 2019

Has been changed to:

Final SAP	28 May 2015
SAP – Amendment 1	10 Feb 2016
SAP – Amendment 2	21 Mar 2019
SAP – Amendment 3	03 Jun 2021

Change #2

List of abbreviations

Added abbreviations for ALT, ALP, AST, BCR, COVID-19, GGT, and LFT.

Change #3

Section 2.2 Study variables

Section 2.2.1 Safety variables

The safety variables include the following:

- Adverse event (AE) reporting
- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, total bilirubin, and gamma-glutamyl transferase [GGT]; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms (ECGs)
- Physical (Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations

- Vital signs (blood pressure and pulse rate)
- Body weight and height

Section 2.2.2 Other safety variables

The other safety variables include the following:

- Change from Baseline in the Achenbach Child Behavior Checklist (CBCL) score: the Achenbach CBCL/1½-5 for children from 1.5 to 5 years of age and the Achenbach CBCL/6-18 for children ≥6 years of age
- Change from Baseline in the Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) score for subjects ≥2 and <5 years of age
- Change from Baseline in the Behavior Rating Inventory of Executive Function (BRIEF) score for subjects ≥5 years of age
- Change from Baseline in the Bayley-III scales in subjects <18 months of age at study entry (applicable only to subjects enrolled in English-speaking countries)

Section 2.2.3 Efficacy variables

The efficacy variables planned for analysis will be based on seizure diary data from EP0034 and will include the following for all subjects:

- Percentage of seizure-free days during the study

Section 2.2.3.1 Other efficacy variables

The following other efficacy variables will be computed for subjects from SP0969:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving LCM in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)

- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL)
- Health care resource use: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays

Has been changed to:

Section 2.2 Study variables

Section 2.2.1 Primary Safety variables

The primary safety variables include the following:

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to study discontinuation

Section 2.2.2 Other safety variables

The other safety variables include the following:

- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyl transferase [GGT]; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms (ECGs)
- Physical (Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations
- Vital signs (blood pressure and pulse rate)
- Body weight and height
- Change from Baseline in the Achenbach Child Behavior Checklist (CBCL) score: the Achenbach CBCL/1½-5 for children from 1.5 to 5 years of age and the Achenbach CBCL/6-18 for children ≥6 years of age
- Change from Baseline in the Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) score for subjects ≥2 and <5 years of age
- Change from Baseline in the Behavior Rating Inventory of Executive Function (BRIEF) score for subjects ≥5 years of age

- Change from Baseline in the Bayley-III scales in subjects <18 months of age at study entry (applicable only to subjects enrolled in English-speaking countries)

Section 2.2.3 Efficacy variables

Section 2.2.3.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

Section 2.2.3.2 Secondary efficacy variables

The secondary efficacy variable planned for analysis will be based on seizure diary data from EP0034 and will include the following for all subjects:

- Percentage of seizure-free days during the study (presented for the overall Treatment Period only)

Section 2.2.3.3 Other efficacy variables

The following other efficacy variables will be computed for subjects from SP0969:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving LCM in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL)
- Health care resource use: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays

Change #4

Section 2.3 Study design and conduct

The following text has been added in this section:

The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

Change #5

Section 2.3 Study design and conduct

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper. A Taper Visit must be completed at the end of the Taper Period.

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the last dose of LCM. A Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the last dose of LCM.

Has been changed to:

Taper Period

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

End of study and Safety Follow-up Period

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the last dose of LCM. A Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the last dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

Change #6

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 EP0034, 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 PedsQL will be presented overall for all applicable subjects and additionally based on the subject's age at Baseline (using the Baseline definition in Section 3.3), using the following age groups:

- ≥1 to ≤12 months
- ≥13 to ≤24 months
- >2 to ≤4 years
- ≥5 to ≤7 years
- ≥8 to ≤12 years
- ≥13 to ≤18 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 EP0034, using the following age groups:

- ≥1 month to <4 years
- ≥4 to <18 years

Summaries for PedsQL will be presented overall for all applicable subjects 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

Change #7

Section 3.2.9 Age at entry and age at first diagnosis

Age at entry into EP0034 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 and date of birth are migrated from the previous pediatric study into the EP0034 SDTM.

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:

Section 3.2.9 Age at entry and age at first diagnosis

Age at entry into EP0034 will be given in years. For subjects with complete date of birth available, age at entry in to EP0034 will use the SDTM derivation definition in the analysis dataset.

For subjects without a complete date of birth available, age at entry into EP0034 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 EP0034)/12.

The age at entry into the previous pediatric study and date of birth are migrated from the previous pediatric study into the EP0034 SDTM.

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

Change #8

Section 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 PedsQL 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 age 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:

Section 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 ≤4 years of age. The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric study 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 age 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.

Change #9

New subsection added for 3.2.24 Age at time of visit/assessment

Change #10

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 #11

Section 3.6 Treatment assignment and treatment groups

Summaries by modal daily dose have been deleted.

Change #12

Section 3.9 Changes to protocol-defined analyses

The sections 3.9.1, 3.9.2, and 3.9.3 have been deleted, as the efficacy endpoints and handing of missing data was added in protocol amendment 2. The subsection numbering of 3.9.4 and 3.95 was updated to 3.9.1 and 3.9.2.

Change #13

Section 5.1 Subject disposition

For the number and percentage of subject completing the study by interval, the ≥12 months category was changed to 12 and ≥24 months.

Change #14

Section 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 #15

Section 6.1 Demographics and other Baseline characteristics

- Age at entry into previous pediatric study (years) (as defined in Section 3.2.9) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years -

  <18 years)
- Age at entry into EP0034 (years) (as defined in Section 3.2.9)
-

Has been changed to:

- Age at entry into previous pediatric study (years) (as defined in Section 3.2.9)
- Age at entry into EP0034 (years) (as defined in Section 3.2.9) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years -<18 years)

Change #16

Section 6.1 Demographics and other Baseline characteristics

Weight at entry to EP0034 was added and weight band updated to use weight at entry to EP0034.

Change #17

Section 6.4.1 Concomitant AEDs taken at the start of the EP0034 Treatment Period

The additional categories for number of AEDs taken at the start of EP0034 were added in: 0 AEDs and 4 AEDs.

Further, the wording preferred name was updated to medication name.

Change #18

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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, select AE tables will also be presented by 3-month time intervals (as defined 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 EP0034 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first EP0034 dose of LCM, or whose intensity worsened on or after the date of first EP0034 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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12, 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 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 enrollment group 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 3-month time intervals (as defined 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 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.

Has been changed to:

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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12 respectively. In addition, select AE tables will also be presented by 3-month time intervals (as defined 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 EP0034 dose of LCM. Treatment-emergent AEs (TEAEs) are defined as those events which started on or after the date of first EP0034 dose of LCM, or whose intensity worsened on or after the date of first EP0034 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 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 enrollment group using the levels defined in Sections 3.2.10 and 3.2.12, respectively.

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

- Incidence of TEAEs
- 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 Section 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 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 enrollment group 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 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 3-month time intervals (as defined 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 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 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, 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 subjects experiencing each TEAE as well as in subject data listings.

Change #19

Section 8.2 Clinical laboratory evaluations

The following text has been added in this section:

The age at the time of assessment will be used for determining TEMA (as defined in Section 3.2.24).

Change #20

Section 8.4.1 Vital signs, body weight, height, BMI, and head circumference

The following text has been added in this section:

The age at the time of assessment will be used for determining MA (as defined in Section 3.2.24).

Change #21

Section 8.4.1 Vital signs, body weight, height, BMI, and head circumference

MA criteria for temperature has been added.

Change #22

Section 8.4.1 Vital signs, body weight, height, BMI, and head circumference

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 subjects with marked bradycardia. Additionally, a subject data listing of all vital signs for subjects 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 subjects with an AE mapped to the PT bradycardia or sinus bradycardia will be presented.

Change #23

Section 8.4.2 Electrocardiograms (ECGs)

The following text has been added in this section:

The age at the time of visit/assessment will be used for determining abnormality criteria (as defined in Section 3.2.24).

Change #24

Section 8.4.7 Achenbach Child Behavior Checklist

The Achenbach CBCL will be completed according to the tabular schedules 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 version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: For subjects who completed the CBCL/1½-5 at the Baseline assessment of the previous study and turn 6 years of age within 1 year after the Baseline assessment of the previous study, the CBCL/1½-5 should be completed for 1 year after the Baseline assessment of the previous study, and subsequently the CBCL/6-18 should be completed.

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.

Table 8–3: CBCL/1½-5

Syndrome scale	Questions
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
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	Questions
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 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:

Section 8.4.8 Achenbach Child Behavior Checklist

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 subjects ≥6 years to ≤18 years, the CBCL/6-18 will be used.

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
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

Table 8–3: CBCL/1½-5

Syndrome scale	Items
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 appropriate scoring spreadsheets.

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.

Change #25

Section 8.4.9.1 BRIEF-P scores

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.

Has been changed to:

Section 8.4.9.1 BRIEF-P scores

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 appropriate scoring spreadsheets.

Raw scores 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 ≥ 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.

Change #26

Section 8.4.9.1 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.

Has been changed to:

Section 8.4.9.1 BRIEF scores

Raw scores 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 the appropriate scoring spreadsheets. 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 will indicate improvement in behavior, 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 from the same questionnaire is available.

Change #27

The subsection 9.2.4.1 Medical procedures has been moved to be after the BRIEF-P and BRIEF assessment subsection and was renumbered to 8.4.11.

Change #28

Section 9.1.1 Percentage of seizure-free days

The percentage of seizure-free days (as defined in Section 3.2.20) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. This will be repeated, separately, by 6-month completer cohorts (as defined in Section 3.2.19) and by seizure type (simple partial, complex partial, or secondarily generalized).

Has been changed to:

Section 9.1.1 Percentage of seizure-free days

The percentage of seizure-free days (as defined in Section 3.2.20) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will also be grouped by enrollment group. This will be repeated, separately by seizure type (simple partial, complex partial, or partial, secondary generalized).

Change #29

Section 9.1.2 Seizure frequency per 28 days

The following analyses will only be done for subjects who participated in SP0969.

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:

Section 9.1.2 Seizure frequency per 28 days

The following analyses will only be done for subjects who participated in SP0969.

Seizure frequency per 28 days (as defined in Section 3.2.13) will be summarized descriptively and presented graphically.

Change #30

Section 9.1.3 Percentage of subjects with ≥50% response to treatment

The following analyses will only be done for subjects who participated in SP0969.

The number and percentage of subjects with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders as defined in Section 3.2.15) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. 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. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. This will be repeated, separately, by 6-month completer cohorts (as defined in Section 3.2.19) and by seizure type (simple partial, complex partial, or secondarily generalized).

Has been changed to:

Section 9.1.3 ≥50% reduction in 28-days partial-onset seizure frequency

The following analyses will only be done for subjects who participated in SP0969.

The number and percentage of subjects with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders as defined in Section 3.2.15) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period.. This will be repeated, separately by seizure type (simple partial, complex partial, or partial, secondary 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.

Change #31

Section 9.1.4 Percentage of subjects with ≥75% response to treatment

The analyses described in Section 9.1.3 for percentage of subjects with ≥50% response to treatment will also be performed for percentage of subjects with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders) for subjects who participated in SP0969.

Has been changed to:

Section 9.1.4 ≥75% reduction in 28-days partial-onset seizure frequency

The analyses described in Section 9.1.3 for percentage of subjects with ≥50% reduction in 28-days partial-onset seizure frequency will also be performed for study subjects with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders) for subjects who participated in SP0969.

Change #32

Section 9.1.5 Absolute and percent reduction in total partial-onset seizures

The following analyses will only be done for subjects who participated in SP0969.

Absolute and percent reduction from Baseline (as defined in Section 3.2.14) in total partial-onset seizures will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. This will be repeated, separately, by 6-month completer cohorts (as defined in Section 3.2.19) and by seizure type (simple partial, complex partial, or secondarily generalized).

Has been changed to:

Section 9.1.5 Absolute and percent reduction in total partial-onset seizures

The following analyses will only be done for subjects who participated in SP0969.

Absolute and percent reduction from Baseline (as defined in Section 3.2.14) in total partial-onset seizures will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will be repeated, separately by seizure type (simple partial, complex partial, or partial, secondary generalized).

Change #33

Section 9.1.6 Percentage of subjects who achieved Seizure-free status

The number and percentage of subjects who achieved seizure-free status (as defined in

Section 3.2.18) will be summarized by seizure time intervals (as defined in Section 3.2.21) and also for the entire Treatment Period. This will be grouped by modal daily LCM dose, using the levels defined in Section 3.2.8. This will be repeated, separately, by 6-month completer cohorts (as defined in Section 3.2.19) and by seizure type (simple partial, complex partial, or secondarily generalized).

Has been changed to:

Section 9.1.6 Seizure-free status

The number and percentage of subjects who achieved seizure-free status (as defined in

Section 3.2.18) will be summarized for the entire Treatment Period. This will be presented by completer cohorts (as defined in Section 3.2.19) and repeated by enrollment groups.

The number and percentage of study 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, or partial, secondary generalized).

Seizure-free status will also be presented by seizure time intervals (as defined in Section 3.2.21) and repeated by enrollment groups. The number and percentage of study subjects 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, partial, secondary generalized).

Change #34

Section 9.2.1 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.

Has been changed to:

Section 9.2.1 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 subjects by Clinical Global Impression of Change value will be summarized by visit and Last Visit . This will be repeated by enrollment group.

Change #35

Section 9.2.2 Caregiver's 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.

Has been changed to:

Section 9.2.2 Caregiver's Global Impression of Change

The Caregiver's 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 subjects by Caregiver's Global Impression of Change value will be summarized by visit and Last Visit. This will be repeated by enrollment group.

Change #36

Section 9.2.3 Pediatric Quality of Life Inventory (PedsQL)

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 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.

Has been changed to:

Section 9.2.3 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.

Section 9.2.3.1 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. This will be repeated by enrollment group. 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.

Section 9.2.3.2 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. This will be repeated by enrollment group. For subjects 5 years and older at Baseline, changes from Baseline will be calculated for all visits, even when the questionnaire version used is different from the one at Baseline. For subjects less than 5 years at Baseline, the change from Baseline will be calculated only when the same questionnaire version is used at Baseline and post-Baseline. All PedsQL >2 years data will be listed.

Change #37

The subsections of 9.2.4 were renumbered as Medical procedures moved to subsection 8.4.11.

Change #38

Section 12.2 Other Significant AEs

The following statement was added: The following MedDRA PTs are defined as other significant TEAEs.

MedDRA preferred terms “Brugada syndrome”, “Cardiac arrest”, “Defect conduction intraventricular”, and “Electrocardiogram QT prolonged” were added. Preferred terms have been arranged in alphabetical order.

Change #39

Section 12.3 List of AEs for Potentially Drug Induced Liver Injury (PDILI)

The following statement was added: The following MedDRA PTs are defined as AEs for Potentially Drug Induced Liver Injury.

MedDRA preferred terms “Alanine aminotransferase increased” and “Aspartate aminotransferase increased” were added. 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.

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