STATISTICAL ANALYSIS PLAN

Study: SP0966

Product: Lacosamide

A MULTI-CENTER, OPEN-LABEL, EXPLORATORY STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN SUBJECTS ≥1 MONTH TO <18 YEARS WITH EPILEPSY SYNDROMES ASSOCIATED WITH GENERALIZED SEIZURES

SAP/Amendment Number	Date
Final SAP	28 Apr 2015
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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
Bayley-III	Bayley Scales of Infant and Toddler Development®, Third Edition
BMI	body mass index
BP	blood pressure
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
CBCL	Child Behavior Checklist
CV	coefficient of variation
DEM	Data Evaluation Meeting
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
ER	emergency room
ET	Early Termination
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GEC	Global Executive Composite
ILAE	International League Against Epilepsy
LCM	lacosamide
LH	luteinizing hormone
MedDRA®	Medical Dictionary for Regulatory Activities
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PT	preferred term
PK-PPS	Pharmacokinetic Per Protocol Set
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SPD	Specification of Protocol Deviations
SS	Safety Set

T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TSH	thyroid stimulating hormone
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report for SP0966.

2 PROTOCOL SUMMARY

Protocol Date: 30 May 2012

Amendment 1: 19 Oct 2012

Amendment 2: 09 Nov 2012

Amendment 3: 21 Jun 2013

Amendment 4: 25 Feb 2014

Amendment 5: 26 Feb 2015

2.1 Study objectives

The objectives of this study are:

- To evaluate the safety and tolerability of lacosamide (LCM) when added to 1 to 3 concomitant antiepileptic drugs (AEDs) in pediatric subjects with epilepsy syndromes associated with generalized seizures
- To obtain preliminary efficacy data of LCM on seizure frequency in pediatric epilepsy syndromes associated with generalized seizures
- An additional objective is to evaluate the pharmacokinetic (PK) of LCM in subjects ≥1 month to <18 years of age.

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

The primary variables assessing safety are:

- Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 to Visit 6
- Change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic clonic, atonic, partial evolving to secondarily generalized) per 28 days from the Baseline Period to the Maintenance Period

The assessment of seizure days will be based on the seizure diary.

2.2.1.2 Secondary safety variables

The secondary variables assessing safety are:

- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 6

- Adverse events (AEs) as reported spontaneously by the subject and/or caregiver, or observed by the investigator
- Subject withdrawals due to AEs

2.2.1.3 Other variables assessing safety

The other safety variables are:

- Changes in hematology, clinical chemistry, and urinalysis parameters
- Changes in hormone status (follicle stimulating hormone [FSH], luteinizing hormone [LH], triiodothyronine [T3], thyroxine [T4], thyroid stimulating hormone [TSH], and testosterone, as appropriate)
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate)
- Physical and neurological examination findings
- Changes in body weight, height, and calculated body mass index (BMI)
- Changes in Tanner Stage (if applicable)
- Behavioral assessment (Achenbach Child Behavior Checklist [CBCL/1½-5 or CBCL/6-18]) for pediatric subjects ≥18 months of age

2.2.1.4 Exploratory Safety variables

- Decrease in generalized spike-wave discharges on 24-hour ambulatory EEG by syndrome subgroups

2.2.2 Efficacy variables

2.2.2.1 Preliminary efficacy variables

Variables used to assess preliminary efficacy will include:

- Change in days with absence seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with myoclonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with tonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with tonic-clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with atonic seizures per 28 days from the Baseline Period to the Maintenance Period

- Change in days with partial evolving to secondarily generalized seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, partial evolving to secondarily generalized) per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with absence seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with myoclonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with tonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with tonic-clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with atonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with partial evolving to secondarily generalized seizures per 28 days from the Baseline Period to the Maintenance Period
- Changes in count of generalized spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 9 or at Early Termination (ET)
- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 9 or at ET
- Clinical Global Impression of Change upon completion of the Maintenance Period (Termination) or at ET
- Caregiver's Global Impression of Change upon completion of the Maintenance Period (Termination) or at ET
- Change in quality of life assessment (Pediatric Quality of Life Inventory [PedsQL™]) for subjects ≥1 month to ≤18 years of age

2.2.2.2 Exploratory efficacy variables

- At least 50 percent reduction in generalized seizures per 28 days by study period (titration and maintenance period) and syndrome subgroup
- Increase in generalized seizures of more than 25 percent per 28 days during the study period by syndrome subgroup
- Percent change in days with any generalized seizures per 28 days during the study period by syndrome subgroup

2.2.3 Pharmacokinetic and pharmacodynamic variables

Plasma concentrations of LCM and concomitant AEDs will be obtained in order to:

- Develop a population PK model of LCM
- Investigate the effect of LCM on the steady-state plasma concentrations of concomitant AEDs
- Investigate the correlation between LCM plasma concentrations and efficacy or safety

2.3 Study design and conduct

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age.

The study treatment is LCM in either the oral solution formulation or tablet formulation. The formulation of LCM to be administered is based on the weight of the subject.

Subjects will not be randomized, but all subjects who sign the informed consent form at Visit 1 will be assigned a unique identification number.

Approximately 50 subjects will be enrolled at approximately 50 sites in Europe, and North America, and other regions as deemed necessary. It is planned to enroll approximately 40 subjects between 4 years and <18 years of age and at least 10 subjects between 1 month and <4 years of age.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period. If all inclusion criteria are met and no exclusion criterion is met, the subject will begin a 6-week Titration Period (LCM dosing flexibility allowed based on tolerability) starting at Visit 2. Subjects will initiate treatment with LCM oral solution at 2mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day (oral solution) for subjects weighing <50kg, or 600mg/day (tablets/oral solution) in subjects weighing ≥50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control.

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. The LCM dose will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study.

The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the ET Visit. Subjects may be eligible for participation in the additional open-label study (SP848). Subjects who choose not to participate in the open-label study or subjects who discontinue due to other reasons will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

A Data Monitoring Committee (DMC) will oversee the safety of the study.

2.4 Determination of sample size

A total of 50 evaluable subjects are planned for enrollment for this study across 2 age groups. The first age group will consist of approximately 40 subjects between 4 years and <18 years of

age. The second age group will consist of at least 10 subjects between 1 month and <4 years of age. Since the primary objective of this open-label exploratory study is to assess the safety and preliminary efficacy of LCM in subjects with generalized seizures and other epilepsy syndromes, a sample size of 50 evaluable subjects is deemed adequate for meeting the objectives of the study. No formal sample size calculations were 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 9.4 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. If not stated otherwise, all summaries will be displayed overall and by age group (≥ 1 month to <4 years, ≥4 to <12 years, and ≥12 to <18 years). For categorical parameters, the number and percentage of subjects in each category will be presented. If not stated otherwise, the denominator for percentages will be based on the number of subjects in the respective population. 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.
- Coefficient of variance (CV[%]) will be presented with 1 decimal place.
- Minimum and maximum will have the same number of decimal places as the original value.

A complete set of data 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 Last dose of LCM

Unless otherwise noted, all references to the last dose of LCM in this SAP refer to the last dose of LCM within the study (eg, including the Taper Period). The last dose of LCM during the Treatment Period will be defined as the last dose during the Titration and Maintenance Periods.

3.2.2 Relative day

The relative day of a visit or an event with respect to the first intake of LCM will be presented in subject data listings. Relative day will be calculated as follows:

- If the visit/event date occurred prior to the first intake of LCM, the relative day is calculated as visit/event date minus first LCM dose date. In subject data listings, relative days based on this situation will be preceded by a '-'.

- If the visit/event date occurred on or after the first intake of LCM but prior to the last dose of LCM, the relative day is calculated as visit/event date minus first LCM dose date + 1.
- If the visit/event date occurred after the date of last dose of LCM, the relative day is calculated as visit/event date minus last dose date. In subject data listings, relative days based on this situation will be preceded by a '+'.

Relative days will not be presented for partial or missing dates.

3.2.3 Study periods

For the purpose of analyses, the following periods are defined.

- Baseline Period:

  The Baseline Period is defined as the period of time from the date of Visit 1 to 1 day prior to the date of first dose of LCM. For the definition of Baseline values see Section 3.3.

- Titration Period:

  The Titration Period is defined as the period of time from the date of first dose of LCM to the date of Visit 6 or the date of ET, whatever occurs first. If Visit 6 and ET are missing the Titration Period ends at the date of last dose of LCM.

- Maintenance Period:

  The Maintenance Period is defined as the period of time from the day after the date of Visit 6 to the date of Visit 9/ET. If Visit 9/ET is missing the Maintenance Period ends at the date of last dose of LCM.

- Treatment Period:

  The Treatment Period is defined as the combined Titration and Maintenance Period, ie, starts at the date of first dose of LCM and ends at Visit 9/ET. If Visit 9/ET is missing the Maintenance Period ends at the date of last dose of LCM.

3.2.4 Last Visit

The Last Visit for all assessments in SP0966 is the last non-missing assessment during the Treatment Period. This cannot be the same assessment as the baseline assessment. 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.

3.2.5 Age and age groups

The age (at enrollment) will be given in years (with 2 decimals) and will be derived with the following formula:

Age (years) = (date of informed consent - date of birth) / 365.25

Partial dates will not be completed. If it is not possible to calculate the age due to incomplete or missing date information the age as documented at Visit 1 will be used:

Age (years) = years part of age in CRF + (month part of age in CRF / 12)

If not stated otherwise, the following age groups will be used for the presentation of results:

- ≥ 1 month to <4 years,
- ≥4 to <12 years, and
- ≥12 to <18 years.

For the derivation of (markedly) abnormal values (see Sections 8.5, 8.6.1, and 8.6.2) the age at assessment will be used. This will be derived as follows:

- For subject with a complete date of birth, use the date of birth to calculate the age at the time of measurement.
- For subject with a partial date of birth with available information about year and month, use the first day of the month to impute the date of birth and use the imputed date of birth to calculate age at the time of measurement.
- For subject with a partial date of birth with available information about year only, use age as given in the eCRF and add the time between measurement and informed consent (ie, [date of measurement – date of informed consent] / 365.25).

3.3 Definition of Baseline values

Unless otherwise specified, Baseline will be based on the last nonmissing data collected prior to the first dose of LCM, ie, assessments on Visit 1 or Visit 2. It is possible that values measured on the day of first dose of LCM (Visit 2 [start of Titration Period]) are assigned to the Baseline Period for summary purposes.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on the primary or secondary safety outcomes or preliminary efficacy outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined separately in the Specification of Protocol Deviations (SPD) document. To the extent feasible, rules for identifying protocol deviations will be 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.

Important protocol deviations will be reviewed as part of the Data Evaluation Meeting (DEM) prior to database lock.

3.5 Analysis sets

The analysis set for subject disposition will be based on All Subjects Screened. Safety variables will be summarized for the Safety Set (SS); efficacy variables will be summarized for the Full Analysis Set (FAS). Select PK analysis may be based on the Pharmacokinetic Per-Protocol Set (PK-PPS). All other parameters will be summarized using the SS.

3.5.1 Safety Set

The primary analysis set will be the SS and will include all enrolled subjects who take at least 1 dose of LCM.

3.5.2 Full Analysis Set

The analysis set for the preliminary efficacy variables will be the FAS and will include all subjects in the SS having had a Baseline and at least 1 post-Baseline efficacy related assessment.

3.5.3 Pharmacokinetic Per Protocol Set

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

3.6 Treatment assignment and treatment groups

All subjects treated in this study receive LCM at doses ranging between 2mg/kg/day (or 100 mg/day) to 12 mg/kg/day (or 600 mg/day). Summaries will be presented based on total number of subjects and will generally not be differentiated by LCM dose. Where appropriate, LCM dose will be presented on subject data listings.

3.7 Center pooling strategy

No data pooling strategies will be applied for analyses for this study. Unless otherwise stated, data from all sites will be combined and summarized collectively.

3.8 Coding dictionaries

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

3.9 Changes to protocol-defined analyses

Not applicable.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

4.2.1 Visit mapping in case of premature discontinuation

Subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. For these subjects, the early termination visit will be mapped to the next scheduled visit, ie, the assessments documented at Visit 9/ET will be assigned to the next scheduled visit, for which the corresponding assessment is scheduled, following the last documented visit.

4.2.2 Missing data

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.

To assess the change and percent change in seizure days for any generalized seizures from the Baseline Period to the Maintenance Period for subjects who prematurely discontinue the study, a

last observation carried forward convention will be applied in the following manner to obtain an estimate for the Maintenance Period:

- Subjects discontinued prematurely during the Titration Period: estimates will be calculated using all available data in the Titration Period and carried forward for the Maintenance Period.
- Subjects discontinued prematurely during the Maintenance Period: estimates will be calculated using all available data in the Maintenance Period and carried forward for the entire Maintenance Period.
- Subjects completing the Maintenance Period: estimates will be calculated using all data from the Maintenance Period.

Missing values for other safety or preliminary efficacy variables will be not imputed.

No imputation of missing values associated with an individual date or visit is planned, with the exception of partial date information for AEs and medications in order to determine whether they are treatment-emergent or concomitant, respectively, and for medical resources to define in which study period these were used. For details see Section 4.2.3.

4.2.3 Incomplete or missing dates for adverse events and concomitant medication

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 in the study or not. For the 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 administration 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 administration 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 date of study termination or the date equivalent to 30 days after last dose of LCM, whatever occurs later.

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

An AE with a completely missing start date will be considered treatment-emergent if the end date of the AE is not on or before the date of first dose of LCM.

With respect to the 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 stop date and a start date prior to the date of last administration of LCM will be considered as concomitant medication. Medications with a missing start date whose stop date is either unknown or after the date of the first application of LCM will be considered as concomitant medication, but not as prior medication. Medications with missing start date whose stop date is prior to first administration of LCM will be considered as prior medication, but not as concomitant medication.

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:

  The last administration date will be imputed for the duration of exposure only as the date of last contact according to the study termination form. A review of the data will be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.

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.

4.3 Interim analyses and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC. The objectives and procedures for the DMC will be detailed in the DMC Charter.

4.4 Multicenter studies

Unless otherwise stated, descriptive summaries for individual sites will not be presented. Subject data listings will provide data grouped by site.

4.5 Multiple comparisons/multiplicity

There will be no adjustment for multiplicity in this study.

4.6 Use of an efficacy subset of subjects

Not applicable.

4.7 Active-control studies intended to show equivalence

Not applicable

4.8 Examination of subgroups

If not stated otherwise, summaries will be presented by age groups as given in Section 3.2.5.

Separate age subgroupings are used for the purpose of summaries of questionnaires with different versions according to the age of the subject. Details are described in the corresponding sections describing the analysis of the questionnaires.

The following syndrome subgroups will be used to investigate AEs and seizure days:

- Infantile spasms/West syndrome
- Lennox Gastaut syndrome
- Dravet Syndrome
- Other symptomatic generalized epilepsy
- Primary generalized epilepsy

The classification of subjects to the syndromes will be done by a medical review and agreed during the DEM. Only subgroups with at least 4 subjects will be presented.

For the presentation of summaries by syndrome subgroups, the syndrome subgroups will be used instead of the age groups, ie, summaries will not be presented by syndrome and age group.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

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

An overall summary of disposition for the SS will present the number and percentage of subjects completing the study and subjects discontinuing along with the reason for discontinuation. This summary will be presented overall as well as for the Titration Period and the Maintenance Period. The disposition summary will be repeated by syndrome subgroups (as described in Section 4.8).

The number and percentage of subjects who discontinued due to AEs broken down by type of AE will be presented overall only (ie, not by age group). The type of AE will be derived by combining outcome (fatal or not) and seriousness (serious or not) of all these AEs (for several AEs, if applicable) as given in the UCB Standard TFL Shells (see Table DS T 04).

The date of first subject in, date of last subject out, number of screened subjects, and the number of subjects in each analysis set (SS, FAS, and PK-PPS) will be summarized overall and by site for all subjects screened. Subjects who transferred sites will be summarized according to their original site. The summary by site will not be presented by age groups.

Additionally, the number and percentage of subjects in the different analysis sets (SS, FAS, and PK-PPS) will be provided.

5.2 Protocol deviations

Important protocol deviations defined in the SPD, and additionally identified at the DEM before database lock, will be listed for the SS.

The number and percentage of subjects with at least 1 important protocol deviation will be summarized overall and by category of important protocol deviation for the SS. The number and percentage of subjects with no important protocol deviations will also be presented in this summary. This summary will not be presented by age group.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

The BMI will be calculated using the formula

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

The following demographics will be summarized for the SS:

- Age (years) – continuous and categorized as (28 days - <24 months, 24 months - <12 years, 12 years - <18 years)
- Gender (male, female)
- Race (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- BMI (kg/m2)
- Head circumference (cm)

The demographics summary will be repeated by syndrome subgroups (as described in Section 4.8).

6.2 Other Baseline characteristics

The time since first diagnosis will be given in years (with 2 decimal places) and will be derived with the following formula:

(Date of informed consent - date of diagnosis) / 365.25

Partial dates will be imputed. If the month and year are available, the diagnosis date is imputed as the later of the following dates: the first day of the month, the subject's birthdate, or the date of the first seizure (if available). If only a year is available, the later of the following dates will be imputed: January 1st of the year, the subject's birthdate, and the date of the first seizure. Completely missing dates will not be replaced and the time since first diagnosis will be set to missing.

The age at first diagnosis will be derived using the same formula as age (see Section 3.2.5) but using the date of first diagnosis of disease instead of the date of informed consent. Partial dates of first diagnosis will be completed as described for the time since diagnosis. If the date of birth is incomplete, the age at first diagnosis will be derived as follows:

- For subject with a partial date of birth with available information about year and month, use the first day of the month to impute the date of birth and use the imputed date of birth to calculate age at first diagnosis.
- For subject with a partial date of birth with available information about year only, use age as given in the eCRF and subtract the time between (imputed) date of diagnosis and informed consent (ie, [date of informed consent – date of diagnosis] / 365.25).

Completely missing dates will not be replaced and the age at first diagnosis will be set to missing.

Antiepileptic drugs will be defined as medications documented on the "Concomitant Medications (AEDs only)" log form. A medical review will be performed to ensure that the medications are documented correctly. Corrective measurements (correction of documentation or programmatic mapping to the correct medication category [AED or not]) will be applied as applicable. Concomitant AEDs at Baseline will be defined as all concomitant AEDs given on the date of first dose of LCM. Medications will be counted only once per unique WHO-DD preferred name.

The following Baseline characteristics will be summarized for the SS:

- Time since first diagnosis (years)
- Age at diagnosis (years)
- History of withdrawal seizures (yes, no)
- History of status epilepticus (yes, no)
- Number of concomitant AEDs at Baseline (1, 2, 3)

The ILAE Seizure classification (1981) history for the last 12 months will be summarized for the SS presenting number and percentage of subjects with the following categories:

- Partial-onset seizures
  - Simple partial with motor signs (I A1)
  - Simple partial with somatosensory or special sensory symptoms (I A2)
  - Simple partial with autonomic symptoms or signs (I A3)
  - Simple partial with psychic symptoms (I A4)

  - Complex partial (I B)
  - Partial evolving to secondarily generalized (I C)
- Generalized seizures
  - Absence (II A)
  - Myoclonic (II B)
  - Clonic (II C)
  - Tonic (II D)
  - Tonic-clonic (II E)
  - Atonic (II F)
- Unclassified epileptic seizures
  - Unclassified epileptic seizures (III)

The historical seizure count form of the electronic Case Report form (eCRF) records the number of seizures per pre-selected ILAE seizure code experienced by the subject during the 4 weeks prior to the start of the study. These data will be provided in a subject data listing.

A listing of reproductive potential and birth control measures for female subjects will be provided.

6.3 Medical history and concomitant diseases

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

6.4 Prior and concomitant medications

Medications will be considered as prior if the start date of the medication is before the date of first dose of LCM. Medications will be considered as concomitant if it was taken at least once during treatment with LCM (ie, from the date of first administration of LCM through the date of last administration of LCM). Medications starting prior to first dose of LCM and continuing during treatment with LCM will be considered both, prior and concomitant medication.

For cases of partial or missing dates the rules described in Section 4.2.3 will be applied.

The number and percentage of subjects taking concomitant AEDs will be summarized by WHO-DD chemical subgroup (Level 4) and preferred drug name for the SS.

The number and percentage of subjects taking prior and concomitant medications (excluding AEDs) will be summarized separately by WHO-DD anatomical main group (Level 1) and therapeutic subgroup (Level 2) for the SS.

Vagus nerve stimulation will only be listed.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

7.1 Derivation of compliance

Actual weight of LCM oral solution will be calculated at each visit using the following formula:

> Actual weight of used oral solution (g) = Total weight of bottles (including caps) at Dispensation - Total weight of bottles (including caps) at Return

The actual weight used will also be determined for the Titration Period, Maintenance Period, and the entire Treatment Period by summing up the respective single actual weights.

The following formula will be used to calculate the expected weight of oral solution for the respective LCM dose:

> Expected weight of used oral solution (g) = Daily prescribed oral solution (mL) x Number of days between visits x 1.1g/mL. (The estimated weight of 1mL of LCM is 1.1g.)

The expected weight will also be determined for the Titration Period, Maintenance Period, and the entire Treatment Period by summing up the respective single expected weights.

A subject's dosing compliance should be within 75-125% during each visit. Compliance to LCM dosing will be calculated for each visit, and will also be determined for the Titration Period, Maintenance Period, and the entire Treatment Period.

For oral solution, compliance will be calculated using the following formula:

> Compliance (%) = Actual weight of used oral solution (g) / Expected weight of used oral solution (g) x 100

For tablets, compliance will be calculated using the following formula:

> Compliance (%) = (100 x [number of 100 mg tablets dispensed – number of 100 mg tablets returned] + 50 x [number of 50 mg tablets dispensed – number of 50 mg tablets returned]) / dose given on the Drug accountability form of the eCRF x number of days)) x 100

7.2 Presentation of compliance

Compliance will be summarized separately for the Treatment Period, the Titration Period and the Maintenance Period. It will be presented with descriptive statistics and additionally categorized as <75%, ≥75% to ≤125%, and >125%

8 SAFETY ANALYSES

All safety analyses will be conducted for the SS.

8.1 Primary safety variables

8.1.1 Generalized spike-wave discharges

The actual values of generalized spike-wave discharges per interpretable hour on 24-hour ambulatory EEG as well as changes from Baseline will be summarized descriptively by visit.

Furthermore, a frequency table will be presented for the number of subjects with an increase of at least 30% and an increase of at least 50% at Visit 6 compared to Baseline.

8.1.2 Generalized seizures

Days with any generalized seizures per 28 days (GSD/28d) will be based on the seizure diary and will be derived separately for the Baseline Period, the Titration Period, and the Maintenance Period. Basis for the calculation will be the number of days with at least 1 generalized seizure (GSD) (absence, myoclonic, clonic, tonic, tonic clonic, atonic, partial evolving to secondarily generalized) during the considered study period and the number of days in the considered study period for which seizure information was provided (D):

GSD/28d = GSD x (28/D)

The days with any generalized seizures per 28 days will only be derived for subjects who completed or discontinued during the respective study period. For subjects who discontinued during the Titration Period, the missing value of the Maintenance Period will be imputed as described in Section 4.2.

Descriptive statistics will be provided for actual values and changes from Baseline for days with any generalized seizures per 28 days by study period. This summary will be repeated by syndrome subgroups (as described in Section 4.8).

8.2 Secondary safety variables

8.2.1 3Hz spike-wave discharges

The actual counts of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG as well as changes from Baseline will be summarized descriptively by visit.

Furthermore, a frequency table will be presented for the number of subjects with an increase of at least 30% and an increase of at least 50% at Visit 6 compared to Baseline.

8.2.2 Adverse events

Treatment-emergent AEs (TEAE) are defined as those events which start on or after the date of first LCM administration and within 30 days following the date of last LCM administration, or whose severity worsens within this time frame.

Other significant AEs are defined in Appendix 13.1 (Table 13-1).

An overall summary of AEs will provide the numbers and percentages of subjects with at least 1 TEAE, serious TEAE, other significant TEAE, TEAE that led to discontinuation, drug-related TEAE, drug-related serious TEAE, severe TEAE, AE leading to death, and TEAE leading to death. The AE overall summary will be repeated by syndrome subgroups (as described in Section 4.8).

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

- TEAEs
- TEAEs during the Titration Period
- TEAEs during the Maintenance Period
- TEAEs by syndrome subgroups (as described in Section 4.8)
- TEAEs including subject numbers

- Serious TEAEs
- Serious TEAEs including subject numbers
- TEAEs leading to discontinuation
- TEAEs leading to discontinuation including subject numbers
- TEAEs by maximum intensity
- Nonserious TEAEs
- Nonserious TEAEs occurring in > 5% of subjects
- Other significant TEAEs

The following summaries by primary SOC and PT will be presented overall only (ie, not by age group).

- TEAEs by relationship to LCM
- Serious TEAEs by relationship to LCM
- Nonserious TEAEs by relationship to LCM
- Fatal TEAEs by relationship to LCM
- Nonserious TEAEs occurring in at least 5% of subjects by relationship

8.3 Exploratory safety variables

A frequency table will be presented for the number of subjects with a decrease of at least 30% and a decrease of at least 50% in generalized spike-wave discharges on 24-hour EEG at Visit 6 compared to Baseline by syndrome subgroups

8.4 Extent of exposure

The duration of LCM exposure for each study period will be calculated as follows:

> Duration of LCM (days) = date of last dose of LCM during the respective period minus the date of first dose of LCM during the respective period plus 1.

For the calculation of the mean daily dose during the Maintenance Period, the total dose for each entry in the LCM administration form with at least 1day within the Maintenance Period will be calculated as follows:

> Total dose = (Morning dose + evening dose) x (administration stop date - administration start date + 1)

If the administration start date is before the start date of the Maintenance Period the start date of the Maintenance Period will be used instead. If the administration stop date is after the end date of the Maintenance Period the end date of the Maintenance Period will be used instead.

The mean daily dose during the Maintenance Period will be calculated as the sum of the total doses for each entry in the study medication administration form with at least 1 day within the Maintenance Period divided by the duration of LCM exposure during the Maintenance Period. Days during an analysis period with unknown dosing will be excluded from both the numerator and the denominator for the calculation of the mean daily dose.

The mean daily dose will be presented in mg/kg/day. For patients who received tablets, the mean daily dose will be normalized by the baseline weight.

The duration of LCM exposure will be summarized with descriptive statistics overall (ie, for the entire Treatment Period) as well as separately for each study period (Titration Period, Maintenance Period).

In addition, the duration of LCM exposure will be summarized in 14-day categories up to the scheduled duration of the period:

- Treatment Period: ≤14 days, >14-≤28 days, >28-≤42 days, >42-≤56 days, >56-≤70 days, >70-≤84 days, >84-≤98 days, >98-≤112 days, >112-≤126 days, >126-≤140 days, >140-≤154 days, >154-≤168 days, and >168 days.
- Titration Period: ≤14 days, >14-≤28 days, >28-≤42 days, and >42 days.
- Maintenance Period: ≤14 days, >14-≤28 days, >28-≤42 days, >42-≤56 days, >56-≤70 days, >70-≤84 days, and >84 days.

The mean daily dose during the Maintenance Period will be summarized descriptively.

8.5 Clinical laboratory evaluations

The following laboratory parameters are measured within the study:

- Hematology: red blood cell count, white blood cell count, differential count (lymphocytes, basophils, eosinophils, monocytes, neutrophils), platelet count, hematocrit, and hemoglobin
- Chemistry: calcium, serum electrolytes (sodium, potassium, chloride, bicarbonate), total protein, albumin, phosphate, glucose, uric acid, alkaline phosphatase, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, total bilirubin, cholesterol, triglycerides
- Urinalysis: albumin, specific gravity, ketones, glucose, pH, microscopic exam for blood cells or casts/high power field
- Endocrinology: FSH, LH, T3, T4, TSH

Markedly abnormal laboratory values are defined in appendix 13.2. Treatment-emergent markedly abnormal (TEMA) values are defined as those markedly abnormal values which occur during the Treatment Period (including unscheduled visits), ie, with a normal Baseline value.

Observed values and changes from Baseline will be summarized for the parameters of hematology, chemistry and endocrinology given above. The Last Visit and minimum and maximum post-Baseline values during the Treatment Period will also be presented in these summaries. Repeated or unscheduled laboratory assessments during the study will not be presented in the by-visit summaries, but will be considered when determining the Last Visit, minimum post-Baseline value, and maximum post-Baseline value.

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value will be summarized by parameter and visit. Percentages will be based on the number of subjects with a nonmissing value at the respective visit. Additionally, a list of subjects with at least 1 TEMA value will be provided including all laboratory measurements of the respective parameter of the respective subject.

Urinalysis and pregnancy test results will only be listed.

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

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

Markedly abnormal vital signs values are defined in Table 8–1.

Table 8–1: Vital Signs Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	<6m	<100, >180
	6m - <3y	<90, >150
	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 BP (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 BP (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	All	>101 ^{0}F (38.3 ^{0}C)
Body Weight	1 month - <17y	<3% or >97% of the normal body weight growth curve ranges[1] based on gender and the age of subject on date of weight assessment
	≥17y	≥10% change from Baseline (an increase or a decrease)

[1] source: http://www.cdc.gov/growthcharts/html_charts/wtage.htm
BP=blood pressure, m=month, y=year.
A month is defined as 30 days; a year is defined as 365.25 days.

Observed values and changes from Baseline for vital signs (systolic BP, diastolic BP, and pulse rate) will be summarized by visit and position/time point including the Last Visit.

Changes of standing measurements versus supine measurements of systolic BP, diastolic BP, and pulse rate will also be summarized for each visit and time point including the Last Visit.

Observed values and changes from Baseline for body weight, height, BMI, and head circumference will be summarized by visit. The Last Visit will also be presented in this summary.

The number and percentage of subjects with a markedly abnormal value, markedly abnormal low value, and markedly abnormal high value will be presented by visit. Percentages will be based on the number of subjects with a nonmissing value at the respective visit. Additionally, a list of subjects with at least 1 markedly abnormal value will be provided including all vital sign measurements of the respective subject.

8.6.2 Electrocardiograms

Abnormality criteria to be used in the determination of ECG abnormalities are defined in Table 8–2, where increase and decrease are relative to Baseline values:

Table 8–2: Electrocardiogram Abnormality Criteria

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

Table 8–2: Electrocardiogram Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
	6m-<3y	<90, >130
	3y-<12y	<60, >130
	>12y	<50, >120

bpm=beats per minute; m=months; ms=milliseconds; QTc=corrected QT interval; y=years.
A month is defined as 30 days; a year is defined as 365.25 days.

Treatment-emergent ECG abnormalities are defined as values meeting the criteria given in Table 8–2 at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline.

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 results and changes from Baseline in ECG results will be summarized for all visits and the Last Visit.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, will be summarized by visit, including last visit. Percentages will be relative to the number of subjects with an ECG assessment at the respective visit. Subjects are counted 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 (including Last Visit) will also be provided based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant.

The number and percentage of subjects with treatment-emergent ECG abnormalities will be presented by visit and treatment group. 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). Percentages will be based on the number of nonmissing values for the variable and visit. In addition, a listing including all ECG parameter values for subjects meeting any abnormality criteria will be provided.

8.6.3 Physical and neurological examination

Summaries of shift from Baseline to Visit 9/ET will be provided based on categories normal, abnormal, not clinically significant, and abnormal, clinically significant for each of the single neurological examinations. Summaries of shift from Baseline normal to any post-baseline abnormal, clinically significant category for each of the neurological examinations will also be provided. For physical examination, summaries of shift from Baseline normal to any post-baseline abnormal, clinically significant category will be presented.

8.6.4 Tanner stage assessment

The Tanner stage is a measurement for the subject's sexual development used for subjects pubescent at Visit 1. It is a 3-item scale (for females: breasts, pubic hair, and overall stage; and for males: genitals, pubic hair, and overall stage) with 5 possible stages (I, II, III, IV, or V).

Shift tables will be produced showing the change in Tanner stage from Visit 1 to Visit 9/ET by gender for each of the 3 single items. Percentages will be based on the number of subjects with at least 1 nonmissing value at Visit 1 or Visit 9/ET.

8.6.5 Achenbach Child Behavior Checklist

The Achenbach CBCL 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 at Baseline. For subjects ≥6 years to <18 years at Baseline, the CBCL/6-18 will be used. For each subject, the same version that is used at Visit 2 (Baseline) should be used at all following visits.

The CBCL/1½-5 comprises 100 questions and the CBCL/6-18 comprises 120 questions with the response options of:

- 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 as given in Table 8–1.

Table 8–1: 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

The CBCL/6-18 will be grouped according to empirically based syndrome scales as given in Table 8–2.

Table 8–2: 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.

For each questionnaire (CBCL/1½-5 and CBCL/6-18, respectively), calculated T-score values and change from Baseline for each CBCL syndrome as given in Table 8–1 and Table 8–2, respectively, will be summarized by visit. The summaries will be presented by the questionnaire's age groups (18 months to 5 years and ≥6 years to <18 years) instead of the ones defined in Section 3.2.5.

8.6.6 BRIEF-P and BRIEF assessment

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 years of age, respectively. For each subject, the same version (BRIEF-P or BRIEF) that is used at Visit 2 (Baseline) should be used at Visit 9/ET.

8.6.6.1 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 sum up to the raw Global Executive Composite (GEC) score which ranges from 63 to 189. Higher scores are reflecting poorer functioning.

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

Table 8–3: 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}

Table 8–3: BRIEF-P questionnaire scoring

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

MI=Metacognition Index, GEC=Global Executive Composite

Standardized T-scores are determined from each subject's raw GEC, Behavioral Regulation Index (BRI), Metacognition Index (MI), and component scores based on the subject's age and sex. 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 2 indexed scores (BRI and MI), and GEC for the BRIEF-P questionnaire will be summarized by visit for the respective age group (≥2 to <5 years), ie, the age groups as defined in Section 3.2.5 will not be used.

8.6.6.2 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 sum up 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 8–4.

Table 8–4: 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
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
MI	**All from {Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor}**

Table 8–4: BRIEF questionnaire scoring

Scale/Index	Questions
GEC Score	**1-72**

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 based on the subject's age and sex. Tables that map each raw score to the appropriate T-score are provided in the BRIEF Professional Manual and will be reproduced programmatically.

Calculated T-score values and change from Baseline for the 2 indexed scores (BRI and MI), and GEC for the BRIEF questionnaire will be summarized by visit for the respective age group (≥5 years), ie, the age groups as defined in Section 3.2.5 will not be used.

9 ANALYSES OF EFFICACY VARIABLES

All analyses of preliminary efficacy variables will be conducted for the FAS.

9.1 Preliminary Efficacy Variables

9.1.1 Seizure days

Days with seizures per 28 days for each seizure type and study period will be calculated as described for the generalized seizures in Section 8.1.2.

Percent change in seizure days is calculated as the respective seizure days per 28 days during the respective period (Titration Period and Maintenance Period) minus respective seizure days per 28 days during the Baseline Period divided by seizure days per 28 days during the Baseline Period and then multiplied by 100.

Descriptive statistics will be used to summarize the observed values as well as absolute and percent changes from Baseline in seizure days per 28 days by study period (Baseline, Titration, and Maintenance Period, respectively). Summaries will be provided for the following seizure types:

- Any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, partial evolving to secondarily generalized)
- Absence seizures
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Atonic seizures

9.1.2 Clinical global impression of change

The Clinical Global Impression of Change is a 7-point categorical rating scale in which the investigator assesses the subject's change from Baseline in clinical status.

The number and percentage of subjects for each possible response of the Clinical Global Impression of Change will be presented. 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", as well as the "No change" group will be summarized in the same way. Percentages will be based on the number of subjects with nonmissing values.

9.1.3 Caregiver's global impression of change

The Caregiver's Global Impression of Change is a 7-point categorical rating scale in which the caregiver assesses the subject's change from Baseline in clinical status.

The number and percentage of subjects for each possible response of the Caregiver's Global Impression of Change will be presented. 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", as well as the "No change" group will be summarized in the same way. Percentages will be based on the number of subjects with nonmissing values.

9.1.4 Pediatric quality of life inventory

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 Visit 2 (Baseline) should be used at Visit 9/ET.

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 4 weeks, 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.

Each scale score is then calculated as the mean of the corresponding nonmissing items if 50% or more of the items are nonmissing. The same algorithm will 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.

Calculated values and change from Baseline for the total scale score and each of the 4 scale scores will be summarized by visit. For the presentation of the PedsQL summary, the questionnaire's age groups (≥1 month to ≤12 months, ≥13 months to ≤24 months, ≥2 to ≤4 years,

≥5 to ≤7 years, ≥8 to ≤12 years, and ≥13 to ≤18 years) will be used instead of the ones defined in Section 3.2.5.

9.1.5 Health care resource use

To assign the health resources to a specific study period (Baseline, Titration, and Maintenance, respectively), partial or missing dates will be imputed as described for AEs and concomitant medications in Section 4.2.3. Hospital stays will be attributed to study periods based on the admission date.

An event logged on the Hospitalization/ER Visit form of the eCRF where "Emergency room" is marked as initial entry point will be defined as an emergency room (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.

For hospital stays with a discharge date, the duration of each hospital stay will be calculated as the discharge date minus the admission date (Hospitalization/ER Visit Date on the eCRF) plus 1 day. For hospitalizations with either a partial admission or discharge date, the duration of hospital stay will be set to missing. The nonmissing durations of hospital stays will be summed within each of the study periods (Baseline, Titration, and Maintenance, respectively). Should distinct records for hospital stays overlap, then the days during the overlap will only be counted once. Subjects with no hospital stays within a study period will have duration of 0 days for that period. For subjects with hospital stays but no calculable hospital duration, the duration of hospitalization in the respective study period will be missing.

The number of concomitant medical procedures per subject (number of entries in the concomitant procedure form) will be summarized continuously and in categories (0, 1, 2, and 3 or more) for the Baseline Period, the Titration Period, and the Maintenance Period.

The number of healthcare provider consultations per subject will be summarized continuously and in categories (0, 1, 2, 3, 4, and 5 or more) for the Baseline Period, the Titration Period, and the Maintenance Period. In addition, the number and percentage of subjects with at least 1 consultation will be given for general practitioner, specialist physician, nurse, or other by study period.

The number of hospital stays per subject will be summarized continuously and in categories (0, 1, 2, 3, 4, and 5 or more) for the Baseline Period, the Titration Period, and the Maintenance Period. The number and percentage of subjects with specific reasons for a hospital stay (epilepsy, lack of efficacy, AE, elective procedure, and other) will also be summarized for these study periods. Furthermore, the duration of hospital stays will be summarized in categories (0 days, 1 to 5 days, 6 to 10 days, 11 to 15 days, and >15 days) by study period. Descriptive statistics for the number of ER visits within each study period will be presented. These summaries will be repeated by syndrome subgroups (as described in Section 4.8).

9.2 Exploratory Efficacy Variables

The analysis of the exploratory efficacy variable will be conducted for the FAS.

Days with seizures per 28 days for each seizure type and study period will be calculated as described for the generalized seizures in Section 8.1.2. The days with any generalized seizures

per 28 days will only be derived for subjects who completed or discontinued during the respective study period. For subjects who discontinued during the Titration period, the missing value of the maintenance period will be implemented as described in Section 4.2

Descriptive statistics will be used to summarize the proportion of subjects who have at least a 50 percent reduction in generalized seizures per 28 days by study period (Titration and Maintenance Period) and syndrome subgroup.

Descriptive statistics will also be produced to summarize the proportion of subjects who have more than 30% and 50% increase in generalized seizures per 28 days during the study period (Titration and Maintenance Period) by syndrome subgroup.

Descriptive statistics will be produced to summarize the percent change in days with any generalized seizures per 28 days during the study period by syndrome subgroup.

10 PHARMACOKINETICS

10.1 Descriptive statistics of LCM and AED plasma concentrations

The results of LCM plasma concentrations will be described by the method of descriptive statistics: n, >=limit of quantification (LOQ), arithmetic mean, SD, median, geometric mean, and geometric CV. Summary statistics will only be calculated if at least 2/3 of the data are above the lower LOQ. Values <LOQ will be set to LOQ/2 for the determination of summary statistics.

The summary of LCM plasma concentrations will be presented by dose level during the Maintenance Period (dose with the longest duration during the Maintenance Period) and visit. The dose levels will be combined as 4-6 mg/kg/day, 7-8 mg/kg/day, 9-10 mg/kg/day, and 11-12 mg/kg/day.

Other AED plasma concentrations will only be listed.

10.2 Population pharmacokinetics and exposure response

Population pharmacokinetics and exposure-response modeling are not in the scope of the SAP and will be described in separate data analysis plans.

11 OTHER ANALYSES

Data of Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III) and Columbia-Suicide Severity Rating Scale will only be listed. The analysis of the Bayley-III scales data will be performed in the follow-up study, SP848.

12 REFERENCES

Not applicable.

13 APPENDICES

13.1 Significant Adverse Events

Table 13-1: List of other significant AEs

MedDRA Preferred Term
HEPATOTOXICITY RELATED TERMS
Hepatitis toxic
Hepatotoxicity
Drug-induced liver injury
Liver function test abnormal
Alanine aminotransferase increased
Aspartate aminotransferase increased
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

Table 13-1: List of other significant AEs

MedDRA Preferred Term
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 AEs'.

13.2 Marked abnormality criteria for laboratory data

13.2.1 Marked abnormality criteria for hematology data

Table 13–2: 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 >15.0	g/L	≤90 >150
	2y - <17y	g/dL	≤9.5 >16.0	g/L	≤95 >160
	≥17y	g/dL	≤85% of LLN ≥115% of ULN	g/L	≤85% of LLN ≥115% of ULN
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

Table 13–2: Hematology abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
	≥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
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

LLN=lower limit of normal, m=month, RBC=red blood cells, ULN=upper limit of normal, WBC=white blood cells, y=year.
A month is defined as 30 days; a year is defined as 365.25 days.

13.2.2 Marked abnormality criteria for chemistry data

Table 13–3: 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 ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN

Table 13–3: Chemistry abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
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
	≥17y	mg/dL	≥40	mmol/L	≥14.28
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

Table 13–3: Chemistry abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
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
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
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y	mg/dL	>300	mmol/L	>3.39

Table 13–3: Chemistry abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
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

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; dL=deciliter; GGT=gamma-glutamyltransferase; HDL=high density lipoprotein; LDL=low density lipoprotein; L=liter; m=month (a month is defined as 30 days); mg=milligram; mmol=millimoles; µg=microgram; U=unit; ULN=upper limit of normal; y=years (a year is defined as 365.25 days)

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

14.1 Amendment 1

Rationale for the amendment
The SAP has been amended to implement any changes to the planned analyses made during the course of the study since the approval of the previous version of the SAP and to incorporate any clarification to the text.

Modifications and changes

Global changes

The following global changes were applied to SAP version 1.0

- Clarification that 'Last Visit' cannot use the baseline assessment
- Specification that for ECGs, average of all interpretable readings at the visit will be used in summaries
- Change in which questions contribute to which scale in the CBCL/6-18
- Addition of Inhibitory self-control scale to BRIEF-P scoring table
- Addition of question 28 to Pan/organize scale of BRIEF scoring table
- Addition of Psychological Health Summary Score in pediatric quality of life inventory
- LCM plasma concentrations are the only concentrations to be summarized. The presentation of specific dose levels has been added. Other AED concentrations are now only listed
- Changes in the presentation of the Nonserious TEAEs
- Presentation of compliance by visit has been removed
- Addition of two new shift tables, one for single neurological parameters and one for physical examinations
- Addition of summary of proportion of responders greater than 50 percent reduction in generalize seizures per 28 days during the study period by syndrome subgroup
- Change of the name of phosphorus to phosphate, total serum protein to total protein and blood urea nitrogen to urea nitrogen
- Typographical corrections
- Dating and version control
- Addition of exploratory safety variables and its analyses
- Addition of exploratory efficacy variables and its analyses
- Change of some of the section numbers and name

Specific Changes

Change #1

Section 3.2.4 Last Visit

The Last Visit for all assessments in SP0966 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.

Has been changed to:

The Last Visit for all assessments in SP0966 is the last non-missing assessment during the Treatment Period. This cannot be the same assessment as the baseline assessment. 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.

Change #2

Section 8.5.2 Electrocardiograms

The average of all interpretable readings for a measurement will be used for summaries. Observed results and changes from Baseline in ECG results will be summarized for all visits and the Last Visit.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, will be summarized by visit.

Has been changed to:

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 results and changes from Baseline in ECG results will be summarized for all visits and the Last Visit.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, will be summarized by visit, including last visit.

Change #3

Table 8-2 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, 8, 10, 13, 17, 41, 61, 80
Rule-breaking behavior	26, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 101, 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, 56, 56g
Thought problems	9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100
Withdrawn/depressed	42, 65, 69, 75, 102, 103, 111

Has been changed to:

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

Change #4

Table 8-3 BRIEF-P questionnaire scoring

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

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

Has been changed to:

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
MI	**All from {Working Memory and Plan/Organize}**
GEC Score	**1-63**

MI=Metacognition Index, GEC=Global Executive Composite

Change #5

Table 8-4 BRIEF questionnaire scoring

Scale/Index	Questions
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, 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
MI	**All from {Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor}**
GEC Score	**1-72**

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

Has been changed to:

Scale/Index	Questions
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
MI	**All from {Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor}**
GEC Score	**1-72**

MI=Metacognition Index, GEC=Global Executive Composite

Change #6

Section 9.4 Pediatric Quality of Life Inventory

Each scale score is then calculated as the mean of the corresponding nonmissing items if 50% or more of the items are nonmissing. The same algorithm will be used to calculate an overall total scale score (all scales) for each subject.

Has been changed to:

Each scale score is then calculated as the mean of the corresponding nonmissing items if 50% or more of the items are nonmissing. The same algorithm will 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 #7

Section 10.1 Descriptive statistics of LCM and AED plasma concentrations

The results of LCM and other AEDs plasma concentrations will be described by the method of descriptive statistics: n, >=limit of quantification (LOQ), arithmetic mean, SD, median, range, geometric mean, and geometric CV. Summary statistics will only be calculated if at least 2/3 of the data are above the lower LOQ. Values <LOQ will be set to LOQ/2 for the determination of summary statistics.

The summary of LCM and other AEDs plasma concentration will be presented by dose level during the Maintenance Period (dose with the longest duration during the Maintenance Period) and visit.

Has been changed to:

The results of LCM plasma concentrations will be described by the method of descriptive statistics: n, >=limit of quantification (LOQ), arithmetic mean, SD, median, geometric mean, and geometric CV. Summary statistics will only be calculated if at least 2/3 of the data are above the lower LOQ. Values <LOQ will be set to LOQ/2 for the determination of summary statistics.

The summary of LCM plasma concentrations will be presented by dose level during the Maintenance Period (dose with the longest duration during the Maintenance Period) and visit. The dose levels will be combined as 4-6 mg/kg/day, 7-8 mg/kg/day, 9-10 mg/kg/day, and 11-12 mg/kg/day.

Other AED plasma concentrations will only be listed.

Change #8

Section 8.2.2 Adverse Events

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

- TEAEs
- TEAEs during the Titration Period
- TEAEs during the Maintenance Period
- TEAEs by syndrome subgroups (as described in Section 4.8)

- TEAEs including subject numbers
- Serious TEAEs
- Serious TEAEs including subject numbers
- TEAEs leading to discontinuation
- TEAEs leading to discontinuation including subject numbers
- TEAEs by maximum intensity
- Nonserious TEAEs occurring in > 5% of subjects
- Other significant TEAEs

Has been changed to:

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

- TEAEs
- TEAEs during the Titration Period
- TEAEs during the Maintenance Period
- TEAEs by syndrome subgroups (as described in Section 4.8)
- TEAEs including subject numbers
- Serious TEAEs
- Serious TEAEs including subject numbers
- TEAEs leading to discontinuation
- TEAEs leading to discontinuation including subject numbers
- TEAEs by maximum intensity
- Nonserious TEAEs
- Nonserious TEAEs occurring in > 5% of subjects
- Other significant TEAEs

Change #9

Section 8.2.2 Adverse Events

The following summaries by primary SOC and PT will be presented overall only (ie, not by age group).

- Nonserious TEAEs
- TEAEs by relationship to LCM
- Serious TEAEs by relationship to LCM
- Nonserious TEAEs by relationship to LCM

- Fatal TEAEs by relationship to LCM
- Nonserious TEAEs occurring in at least 5% of subjects by relationship

Has been changed to:

The following summaries by primary SOC and PT will be presented overall only (ie, not by age group).

- TEAEs by relationship to LCM
- Serious TEAEs by relationship to LCM
- Nonserious TEAEs by relationship to LCM
- Fatal TEAEs by relationship to LCM
- Nonserious TEAEs occurring in at least 5% of subjects by relationship

Change #10

Section 7.2 Presentation of compliance

Compliance will be summarized separately for the Treatment Period, the Titration Period, the Maintenance Period and each visit for the SS. It will be presented with descriptive statistics and additionally categorized as <75%, ≥75% to ≤125%, and >125%

Has been changed to:

Compliance will be summarized separately for the Treatment Period, the Titration Period and the Maintenance Period. It will be presented with descriptive statistics and additionally categorized as <75%, ≥75% to ≤125%, and >125%

Change #11

Section 8.5.3 Physical and Neurological Examinations

Summaries of shift from Baseline to Visit 9/ET will be provided based on categories normal, abnormal, not clinically significant, and abnormal, clinically significant for each of the single neurological examinations. Examinations at other visits will only be listed.

Has been changed to:

Summaries of shift from Baseline to Visit 9/ET will be provided based on categories normal, abnormal, not clinically significant, and abnormal, clinically significant for each of the single neurological examinations. Summaries of shift from Baseline normal to any post-baseline abnormal, clinically significant category for each of the neurological examinations will also be provided. For physical examination summaries of shift from Baseline normal to any post-baseline abnormal, clinically significant category will be presented.

Change #12

Section 2.2.1.4 Exploratory safety variables

Has been added:

Decrease in generalized spike-wave discharges on 24-hour ambulatory EEG by syndrome subgroups.

Change #13

Section 8.4 Clinical laboratory evaluations

Chemistry: calcium, serum electrolytes (sodium, potassium, chloride, bicarbonate), total serum protein, albumin, phosphorus, glucose, uric acid, alkaline phosphatase, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, total bilirubin, cholesterol, triglycerides

Has been changed to:

Chemistry: calcium, serum electrolytes (sodium, potassium, chloride, bicarbonate), total protein, albumin, phosphate, glucose, uric acid, alkaline phosphatase, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, total bilirubin, cholesterol, triglycerides

Change #14

Section 8.3 Exploratory safety variables

Has been added as a new section

A frequency table will be presented for the number of subjects with a decrease of at least 30% and a decrease of at least 50% in generalized spike-wave discharges on 24-hour EEG at Visit 6 compared to Baseline by syndrome subgroups

Change #15

Section 2.2.2 Preliminary efficacy variables

Has been changed to:

Section 2.2.2 Efficacy variables

Change #16

Section 2.2.2 Preliminary efficacy variables

Has been changed to:

Section 2.2.2.1 Preliminary efficacy variables

Change #17

New section 2.2.2.2 exploratory efficacy variables has been added

Change #18

Section 9 Analyses of Preliminary Efficacy Variables

Has been changed to:

Section 9 Analyses of Efficacy Variables

Change #19

Section 9.1 Seizure days

Has been changed to:

Section 9.1 Preliminary Efficacy Variables

Change #20

Section 9.1 Seizure days

Has been changed to:

Section 9.1.1 Seizure days

Change #21

Section 9.2 Clinical Global Impression of Change

Has been changed to:

Section 9.1.2 Clinical global impression of change

Change #22

Section 9.3 Caregivers Global Impression of Change

Has been changed to:

Section 9.1.3 Caregivers global Impression of change

Change #23

Section 9.4 Pediatric Quality of Life Inventory

Has been changed to:

Section 9.1.4 Pediatric quality of life inventory

Change #24

Section 9.5 Health care resource use

Has been changed to:

Section 9.1.5 Health care resource use

Change #25

New section 9.2 Exploratory Efficacy Variables

Has been added:

The analysis of the exploratory efficacy variable will be conducted for the FAS.

Days with seizures per 28 days for each seizure type and study period will be calculated as described for the generalized seizures in Section 8.1.2. The days with any generalized seizures per 28 days will only be derived for subjects who completed or discontinued during the

respective study period. For subjects who discontinued during the Titration period, the missing value of the maintenance period will be implemented as described in Section 4.2

Descriptive statistics will be used to summarize the proportion of subjects who have at least a 50 percent reduction in generalized seizures per 28 days by study period (Titration and Maintenance Period) and syndrome subgroup.

Descriptive statistics will also be produced to summarize the proportion of subjects who have more than 30% and 50% increase in generalized seizures per 28 days during the study period (Titration and Maintenance Period) by syndrome.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

SP0966 - SAP Amendment 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	06-Mar-2018 17:53 GMT+01
	Clinical Approval	06-Mar-2018 19:16 GMT+01