

# STATISTICAL ANALYSIS PLAN

**Study: SP0969**

**Product: Lacosamide**

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN SUBJECTS WITH EPILEPSY  $\geq 4$  YEARS TO  $< 17$  YEARS OF AGE WITH PARTIAL-ONSET SEIZURES

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## LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANCOVA	analysis of covariance
bid	twice daily
BMI	body mass index
BP	blood pressure
BRIEF <sup>®</sup>	Behavior Rating Inventory of Executive Function <sup>®</sup>
BRIEF <sup>®</sup> -P	Behavior Rating Inventory of Executive Function <sup>®</sup> - Preschool Version
CBCL	Child Behavior Checklist
CI	confidence interval
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTStat	Clinical Trial Biostatistician
CV	coefficient of variation
DAP	Data Analysis Plan
DBP	diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	electrocardiogram
eCRF	electronic Case Report form
ETV	Early Termination Visit
FAS	Full Analysis Set
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
IVRS	Interactive Voice Response System
LCM	lacosamide
LSM	least squares mean
MA	markedly abnormal
MedDRA <sup>®</sup>	Medical Dictionary for Regulatory Activities

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PBO	placebo
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PT	preferred term
SBP	systolic blood pressure
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SPD	Specification of Protocol Deviations
SS	Safety Set
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
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 SP0969.

## 2 PROTOCOL SUMMARY

### 2.1 Study objectives

#### 2.1.1 Primary objective

- To evaluate the efficacy of lacosamide (LCM) administered concomitantly with 1 to  $\leq 3$  antiepileptic drugs (AEDs) in subjects with epilepsy  $\geq 4$  years to  $< 17$  years of age who currently have uncontrolled partial-onset seizures

#### 2.1.2 Secondary objective

- To evaluate the safety and tolerability of LCM in subjects  $\geq 4$  years to  $< 17$  years of age

#### 2.1.3 Other objective

- To evaluate the pharmacokinetics (PK) of LCM in subjects  $\geq 4$  years to  $< 17$  years of age

### 2.2 Study variables

#### 2.2.1 Efficacy variables

The assessment of efficacy is based on partial-onset seizure frequency.

##### 2.2.1.1 Primary efficacy variable

The primary efficacy variable is:

- Change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period

##### 2.2.1.2 Secondary efficacy variables

The secondary efficacy variables include the following:

- Proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in partial-onset seizure frequency from Baseline to the Maintenance Period
- Proportion of subjects experiencing a  $\geq 25\%$  to  $< 50\%$ , 50% to 75%, or  $> 75\%$  reduction in partial-onset seizure frequency from Baseline to the end of Maintenance Period
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing a  $\geq 25\%$  to  $< 50\%$ , 50% to 75%, or  $> 75\%$  reduction in partial-onset seizure frequency from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing no change in partial-onset seizure frequency (between  $< 25\%$  reduction and  $< 25\%$  increase) from Baseline to the entire treatment (ie, Titration+Maintenance Periods)

- Proportion of subjects experiencing an increase in partial-onset seizure frequency of  $\geq 25\%$  from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods) by seizure type
- Proportion of seizure-free days during the Maintenance Period for subjects who entered the Maintenance Period
- Proportion of subjects who achieved “seizure-free” status (yes/no) for subjects who completed the Maintenance Period

### **2.2.1.3 Other efficacy variables**

Other efficacy variables to be examined include:

- Clinical Global Impression of Change at the end of the Maintenance Period
- Caregiver’s Global Impression of Change at the end of the Maintenance Period
- Quality of life assessments (PedsQL)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol)

### **2.2.2 Safety variables**

#### **2.2.2.1 Primary safety variables**

Safety and tolerability will be assessed using the following primary variables:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver (including parent/legal guardian) or observed by the investigator
- Subject withdrawals due to AEs

#### **2.2.2.2 Other safety variables**

The other safety variables include:

- Changes in hematology, clinical chemistry, and endocrinology parameters
- 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
- Behavioral assessments (Achenbach Child Behavior Checklist/1½-5 [CBCL/1½-5] or CBCL/6-18)
- Cognitive function assessments (BRIEF-P/BRIEF)

### **2.2.3 Pharmacokinetic 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

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day [oral solution] for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day [oral solution] for subjects weighing  $\geq$ 30kg to <50kg, and LCM 300mg/day to 400mg/day [tablets] for subjects weighing  $\geq$ 50kg, or matching placebo) as adjunctive therapy in subjects with epilepsy  $\geq$ 4 years to <17 years of age with uncontrolled partial-onset seizures. Subjects weighing  $\geq$ 50kg who are unable or unwilling to swallow tablets may receive LCM oral solution. However, they are not permitted to exceed the maximum dose of LCM 400mg/day.

A total of approximately 300 subjects are planned to be randomized at approximately 155 sites. The study will be conducted in the [REDACTED] region with the possibility to expand the study to other countries and regions if deemed necessary.

Stratification of subjects by age category is planned to ensure that an appropriate number of subjects will be included in each age range. The age categories are as follows:

- At least 100 subjects  $\geq$ 4 years to <12 years of age
- At least 100 subjects  $\geq$ 12 years to <17 years of age

Subjects with uncontrolled partial-onset seizures will be enrolled into an 8-week Baseline Period. At the end of the Baseline Period (Visit 2), eligible subjects will be randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or placebo in a 1:1 ratio. At the end of Visit 2, subjects should take the first dose of study medication while in the clinic. At each subsequent clinic visit, subjects should take study medication (and any concomitant AEDs) at the regular times. Study medication will be administered orally bid at approximately 12-hour intervals in the morning and in the evening.

Eligible subjects will enter a 6-week Titration Period (with study medication dosing flexibility allowed based on tolerability) to achieve the target Maintenance Period dose (LCM 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for subjects weighing  $\geq$ 30kg to <50kg, and LCM 300mg/day to 400mg/day for subjects weighing  $\geq$ 50kg, or matching placebo). Subjects must achieve the minimum target dose for their body weight category for the final 3 days of the Titration Period to be eligible for entry into the Maintenance Period. If it becomes apparent that a subject will not be able to reach the minimum target dose, then the subject should be withdrawn from the study and enter the Taper Period.

Subjects who achieved at least the minimum target study medication (LCM or matching placebo) dose for the final 3 days of the Titration Period will enter a 10-week Maintenance Period on the study medication dose achieved on the final day of the Titration Period. Lacosamide dose (or matching placebo) will remain stable throughout the Maintenance Period. Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will enter the blinded Transition Period. Subjects who require a change in dose during the

Maintenance Period will be withdrawn and enter the blinded Taper Period. Subjects who choose not to participate in EP0034 will also enter the Taper Period.

Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will enter a 4-week blinded Transition Period. Subjects randomized to LCM will maintain their Maintenance Period dose during the Transition Period. Subjects randomized to placebo will transition to LCM in a double-blind fashion in accordance with the schedule provided in Table 7-4 of the protocol.

The blinded Taper Period (2 to 4 weeks, depending on dose level achieved) is for subjects who will not be entering the open-label extension study (EP0034) for any of the following reasons:

- Subject does not complete the Titration Period, the Maintenance Period, or the Transition Period
- Subject does not choose to enroll in the open-label extension study (EP0034) after completing the Maintenance Period or the Transition Period

Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

The dosing of study medication for the Taper Period is provided in Table 7-5 of the protocol .

There will be a 30-day Safety Follow-Up Period for subjects not entering the open-label extension study (EP0034).

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

Each subject's total duration of study medication administration is up to 24 weeks. The total study duration can be up to 36 weeks, including the 30-day safety Follow-Up Period.

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

Assuming an effect size of 0.342, in which the effect size was calculated using a placebo-subtracted difference of -0.249 and a common SD of 0.73 on the log-transformed data, the difference of -0.249 on the log-transformed data is equivalent to approximately 22% reduction over placebo after exponentiation. With this effect size, power of 80%, and a 2-sided test at the 5% level of significance, a sample of 135 subjects in each treatment arm will be needed.

Assuming a responder rate of 22% and 40% for the placebo and LCM groups, respectively, a 2-sided continuity corrected Chi-square test at a significance level of 5% will provide approximately 87% power with 135 subjects in the placebo group and 135 subjects in the LCM group.

To account for an anticipated subject dropout rate of approximately 14%, the planned number of subjects to enroll is 154 subjects per treatment arm.

### 2.4.1 Blinded sample size re-estimation procedure

After 50% of subjects have been randomized, completed the study (including those who discontinued), and have Baseline and post-Baseline seizure data available for analysis, a sample size re-estimation procedure will be performed in 2 consecutive stages of adjustment:

- Stage 1: Initial sample size re-estimation. An initial sample size re-estimation with equal allocation in each treatment arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011) to give a revised sample size to be adjusted in Stage 2 and Stage 3. This value will not be adjusted by more than 10% above the current estimate of 135 subjects per treatment arm (ie, the initial sample size re-estimate will not be adjusted above 149 subjects per treatment arm).
- Stage 2: Adjustment for drop-out rate. The overall study drop-out rate will be determined. The current SP0969 protocol plans for a 14% overall study drop-out rate for use in determination of sample size. If the actual overall study drop-out rate is >14%, UCB plans to adjust the sample size from Stage 1 accordingly, using an overall study drop-out rate up to a maximum of 24% (ie, the original estimated overall study drop-out rate can be increased by a maximum of 10%).

## 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 9.3. 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.
- 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.

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as “<0.0001” and p-values greater than 0.9999 will be presented as “>0.9999.” Statistical comparison will be performed at the 0.0500 level of significance.

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 Analysis time points**

#### **3.2.1.1 Last dose of study medication**

Unless otherwise noted, all references to the last dose of study medication in this SAP refer to the last dose of study medication taken across all study periods (ie, the last dose of study medication across the Titration, Maintenance, Transition, and Taper Periods). The last dose of study medication during the Treatment Period will be defined as the last dose during the Titration and Maintenance Periods.

#### **3.2.1.2 Relative day**

Relative day will be calculated as the current date minus the date of first dose of study medication plus 1 for days on or after the day of first dose of study medication and prior to or on the day of last study medication dose (eg, the day of first dose will be Day 1.) Relative day will be calculated as the current date minus the date of first dose of study medication for days prior to the first dose of study medication (the day prior to first dose will be Day -1). For days after the last dose of study medication, relative day will be calculated as the current date minus the date of last dose of study medication 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**

The study consists of the following six periods: Baseline Period, Titration Period, Maintenance Period, Transition Period, Taper Period, and Safety Follow-Up Period. Additionally for analysis purposes, the Treatment Period includes Titration and Maintenance Periods. Each period is defined in turn as follows for the classification by study period:

#### Baseline Period

On or after the date of Visit 1 (entry to study) and prior to the date of first dose of study medication.

#### Titration Period

On or after the date of first dose of study medication and prior to or on the end date of the Titration Period (Visit 5) for subjects who complete the Titration Period, or on or after the date of first dose of study medication and prior to or on the date of the Early Termination Visit (ETV) for subjects who discontinue during the Titration Period. If a subject does not have a Visit 5/ETV, then either the date of the last scheduled or unscheduled visit during the Titration Period or the date of last known dose of study medication during the Titration Period, whichever is later, will define the end date of the Titration Period.

#### Maintenance Period

The day after the end of the Titration Period (Visit 5) and prior to or on the end date of the Maintenance Period (Visit 8) for subjects who complete the Maintenance Period, or the day after the end of the Titration Period (Visit 5) and prior to or on the date of the ETV for subjects who

discontinue during the Maintenance Period. If a subject does not have a Visit 8/ETV, then either the date of the last scheduled or unscheduled visit during the Maintenance Period or the date of last known dose of study medication during the Maintenance Period, whichever is later, will define the end date of the Maintenance Period.

#### Treatment Period

On or after the date of first dose of study medication and prior to or on the end date of the Treatment Period (Visit 8) for subjects who complete the Treatment Period, or on or after the date of first dose of study medication and prior to or on the date of the ETV for subjects who discontinue during the Treatment Period. If a subject does not have a Visit 8/ETV, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of study medication during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

#### Transition Period

For those subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034), the Transition Period is defined as the date after the last dose of study medication in the Maintenance Period and prior to enrollment into EP0034.

#### Taper Period

For those subjects who discontinue study medication or for those subjects who complete the Maintenance Period but choose not to enter EP0034, the Taper Period is defined as the date after the last dose of study medication in the Titration, Maintenance or Transition Periods, as appropriate, and the date of last dose of study medication.

#### Safety Follow-Up Period

There will be a 30-day Safety Follow-Up Period for subjects not entering EP0034. The Safety Follow-Up Period is defined as the date after the last dose of study medication in SP0969 and continues until the date of last telephone contact and/or 30 days after the last dose of study medication, whichever is later.

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

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

In particular, clinical laboratory parameters, vital signs, and body weight are assessed at all visits during the Treatment Period, and so all assessments of these variables at ETVs corresponding to a scheduled visit will be mapped to the corresponding scheduled visit.

### **3.2.4 Last Visit**

The Last Visit for all assessments 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.

### 3.3 Definition of Baseline values

In general, Baseline values for efficacy and safety variables will be determined from the last non-missing scheduled or unscheduled assessment prior to the first dose of study medication, unless otherwise noted for a specific type of data.

### 3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary efficacy outcome or key safety 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 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 blinded Data Evaluation Meetings (DEMs) prior to unblinding of the database. A list of subjects with important protocol deviations will be agreed upon during the DEMs and will be documented in the DEM minutes.

### 3.5 Analysis sets

The analysis sets defined for this study are the Safety Set (SS), Full Analysis Set (FAS), Per Protocol Set (PPS), and Pharmacokinetic Per Protocol Set (PK-PPS).

The primary analysis for the efficacy data will be the FAS. The secondary analysis set for the efficacy data will be the PPS. The primary analysis set for the safety parameters is the SS. The primary analysis set for the PK parameters is the PK-PPS.

#### 3.5.1 Safety Set

The SS will include all randomized subjects who took at least 1 dose of study medication.

#### 3.5.2 Full Analysis Set

The FAS will include all subjects who were randomized, received at least 1 dose of study medication, and had a Baseline and at least 1 post-Baseline assessment of seizure frequency data.



### **3.5.3 Per Protocol Set**

The PPS includes all subjects in the FAS who did not have important protocol deviations considered to have an impact on efficacy as confirmed during a DEM conducted prior to study unblinding.

### **3.5.4 Pharmacokinetic Per Protocol Set**

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

## **3.6 Treatment assignment and treatment groups**

It is expected that subjects will receive treatment as randomized. Thus, treatment assignment for the FAS and the SS will be according to randomization. However, if after unblinding it is determined that the subjects received treatment other than what they were randomized to receive, the safety analyses will be conducted using treatment assignments according to the actual treatment received (SS-as treated).

All subjects treated in this study receive study LCM at doses ranging from 8mg/kg/day to 12mg/kg/day (oral solution) for subjects weighing <30kg, 6mg/kg/day to 8mg/kg/day (oral solution) for subjects weighing  $\geq$ 30kg to <50kg, 300mg/day to 400mg/day (tablets) for subjects weighing  $\geq$ 50kg, or matching placebo. The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study. Summaries will be presented based on treatment group; Placebo and LCM, and will generally not be differentiated by LCM dose. Where appropriate, LCM dose will be presented in subject data listings.

### **3.7 Center pooling strategy**

All centers will be pooled by country for the purpose of analysis.

### **3.8 Coding dictionaries**

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup> 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**

There are no changes to analyses specified in the protocol.

## **4 STATISTICAL/ANALYTICAL ISSUES**

### **4.1 Adjustments for covariates**

An analysis of the primary efficacy variable and analyses of several other efficacy variables will be adjusted for Baseline seizure frequency and pooled center.

### **4.2 Handling of dropouts or missing data**

#### **4.2.1 Missing data**

For subjects who discontinue prior to the Maintenance Period, all available seizure frequency data will be carried forward from the Titration Period for the Maintenance Period analysis. For subjects who prematurely discontinue during the Maintenance Period, all available seizure

frequency data in the Maintenance Period will be carried forward for the entire Maintenance Period.

Subjects who discontinue prior to any efficacy data collection will not be included in the analysis (ie, data will not be carried forward from Baseline). The imputation for the seizure frequency data will not carry forward into the Transition and Taper Periods.

No imputation of missing values associated with an individual date or visit is planned for the primary safety analysis, with the exception of partial date information for AEs and concomitant medications in order to determine whether the AEs are treatment-emergent or the medications are concomitant.

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to study medication per the investigator will be assumed to be related. Incomplete or missing dates for events will be handled as described in section 3.2.2.

#### **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 study medication 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 study medication. 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 study medication 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 study medication. 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 study medication.

However, if the study termination year and year for the date which is 28 days after last intake of study medication 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, excluding AEDs, with a missing start date whose stop date is either unknown or after the date of the first dose of study medication will be considered as concomitant medication.

AEDs with a missing start date whose stop date is unknown will be considered as lifetime AEDs. AEDs with a missing start date whose stop date is after the date of first dose of study medication will be considered concomitant.

Medications, including AEDS, with a missing start date whose stop date is prior to first intake of study medication 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 study medication**

For purposes of imputing missing components of partially reported dates for the last administration of study medication, the algorithms listed below will be followed. Stop dates of study medication 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.

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. If more than 10% of the diary entries are missing for a specific subject and time interval, then that subject will not be considered for the calculation of seizure frequency or seizure-free days during that time interval.

#### **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 study medication
- 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 informal interim analysis for determination of efficacy is planned for this study. To ensure subject safety, interim reviews of the safety data will be performed using an Independent Data monitoring Committee (IDMC). Serious adverse events and other significant events (detailed in Appendix 12 (section 12.2)) are monitored and will be triaged by the medical monitor and UCB Drug Safety in real time. After this triage, events will be passed on to the IDMC as appropriate. In addition, 3 interim reviews of safety data by the IDMC are planned when 25%, 50%, and 75% of subjects have been randomized and at study completion. Study enrollment will not be halted during planned IDMC review of the safety data. The objective, procedures, and timing of the IDMC safety assessments to evaluate risk and benefit for subjects in SP0969 will be described in the IDMC Charter.

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study (including those who discontinued), and have Baseline and post-Baseline seizure data available for analysis. See section 2.4.1 for details.

### **4.4 Multicenter studies**

This is a multicenter study. It is planned to appropriately pool centers by geographic location. The final strategy for pooling will be determined at the final DEM prior to unblinding the study.

Treatment by center interactions will be explored in the analysis.

### **4.5 Multiple comparisons/multiplicity**

There will be no adjustment for multiplicity in this study.

### **4.6 Use of an efficacy subset of subjects**

The primary efficacy variable will also be analyzed for the PPS. This analysis set will provide additional information on the analysis of the primary efficacy variable and the impact of the important protocol deviations on efficacy.

Other than the planned analyses based on the PPS, no other efficacy subsets are defined for statistical analyses.

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

This section is not applicable for this study.

### **4.8 Examination of subgroups**

Age at enrollment will be categorized into the subgroups:  $\geq 4$  to  $< 12$  years, and  $\geq 12$  to  $< 17$  years and used within summaries of disposition, demography, exposure, adverse events and certain efficacy analyses. Weight at Baseline will be categorized into the subgroups:  $< 30$ kg,  $\geq 30$ kg to

<50kg, and  $\geq$ 50kg, and used within summaries of exposure and adverse events. Further detail of these summaries is provided within the relevant subsections of sections 8 and 10.

Separate age subgroupings are used for the purpose of PedsQL summaries, and are detailed in section 8.3.3.

## **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 overall and repeated by age group, using the levels defined in section 4.8.

An overall summary of disposition for the SS will present the number and percentage of subjects randomized in the study, subjects completing the study, and subjects discontinuing along with the reason for discontinuation by treatment group and overall. This will be repeated for subjects in the FAS and also repeated by treatment group and age group for the SS.

In addition, an overall summary of disposition for the SS, as described above, will be broken down by study period (Titration, Maintenance, Transition and Taper Periods), treatment group and overall.

The date of first subject in, date of last subject out, number of enrolled subjects, and the number of subjects randomized, number of subjects in each treatment group, and overall, and the number of subjects in each analysis set (SS, FAS, PPS and PK-PPS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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 subjects data listings.

### **5.2 Protocol deviations**

Important protocol deviations defined in the important protocol deviation document, and additionally identified at the DEMs before unblinding of the database 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 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**

For subjects who only have a year of birth reported based on region-specific regulations, age will be obtained from the Interactive Voice Response System (IVRS) used to randomize subjects. Otherwise, age will be calculated relative to the date of informed consent. Weight will be summarized from Visit 1.

Body mass index (BMI) will be calculated using the subject weight recorded at Visit 1 (at study entry) as:

$$\text{BMI} = \text{weight in kilograms} / (\text{height in meters})^2$$

Age, age category ( $\geq 4$  to  $< 12$ , and  $\geq 12$  to  $< 17$  years of age), EudraCT age category ( $\geq 24$  months to  $< 12$  years, and  $\geq 12$  to  $< 18$  years), gender, weight (kg), weight band ( $< 30$ ,  $\geq 30$  to  $< 50$ ,  $\geq 50$  kg), height (cm), BMI ( $\text{kg}/\text{m}^2$ ), 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), and vagus nerve stimulation (VNS) use (Active VNS, No VNS, and VNS not active) will be summarized by treatment group and overall for the SS, and repeated by treatment group and age group, using the levels defined in section 4.8.

A listing of reproductive potential and birth control measures for female subjects will be provided. No summaries of these findings 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, including both resolved and ongoing conditions at the time of study entry, will be summarized overall and by MedDRA<sup>®</sup> primary system organ class (SOC) and preferred term (PT) by treatment group for the SS.

Subjects who had any procedures of surgeries prior to study entry will be listed.

### **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) will be summarized by SOC and PT for subjects in each treatment group for the SS.

## **6.3 History of epilepsy**

### **6.3.1 History of seizure types**

The number and percentage of subjects experiencing each seizure type (partial-onset seizures, generalized seizures, and unclassified epileptic seizures) at any time prior to study entry will be summarized by treatment group for the SS based on the ILAE Seizure Classification History eCRF.

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 evolving to secondarily generalized (IC) seizures. A subject will be classified as having a history of generalized seizures if the subject has a history of absence (IIA1), atypical absence (IIA2), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), and atonic (IIF) seizures.

### **6.3.2 History of seizure characteristics**

History of epileptic seizures, including the number and percentage of subjects with a history of withdrawal seizures, number and percentage with a history of status epilepticus, and with quantitative summaries of epilepsy duration and age at diagnosis will be summarized by treatment group for the SS.

The date of first diagnosis collected in the eCRF only includes month and year; the 1<sup>st</sup> of the month will be imputed for calculating epilepsy duration. The age at first diagnosis will be imputed using the 1<sup>st</sup> of the month or the subject's date of birth, whichever is later, if only the month and year are known, or January 1 of the same year or the subject's date of birth, whichever is later, if only the year is known.

### **6.3.3 Historical seizure count**

The historical seizure count eCRF records the number of seizures per pre-selected ILAE seizure code experienced by the subject during the 8 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 will be attributed to the study periods as defined in section 3.2.2 based on the start date of the medication.

### **6.4.1 Number of Lifetime AEDs**

The number of lifetime AEDs defined as AEDs taken and stopped >28 days prior to Visit 1 (ie, prior to entry into the Baseline Period), or AEDs with a missing start date and unknown stop date, will be summarized by treatment group and overall for the SS based on the following categorization: 0 AEDs, 1 to 3 AEDs, 4-6 AEDs, and  $\geq 7$  AEDs.

### **6.4.2 Number of AEDs taken prior to the Baseline Period**

The number of AEDs taken prior to the Baseline Period defined as AEDs with a start date prior to the date of informed consent, ie, prior to entry into the Baseline Period, excluding lifetime AEDs, will be summarized by treatment group and overall for the SS based on the following categorization: 1 AED, 2 AEDs, and 3 AEDs.

The number and percentage of subjects taking AEDs prior to the Baseline Period will be summarized by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

### **6.4.3 AEDs taken during the Baseline Period**

The number and percentage of subjects taking AEDs during the Baseline Period defined as AEDs with a start date on or after the date of informed consent and prior to the first dose of study medication, and AEDs with a start date prior to the date of informed consent and with a stop date on or after the start of the Baseline Period, will be summarized, separately, by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

### **6.4.4 Number of AEDs taken on day of first dose of study medication**

The number of AEDs taken on the day of first dose of study medication will be summarized by treatment group and overall for the SS based on the following categorization: 1 AED, 2 AEDs, and 3 AEDs.

#### 6.4.5 Concomitant AEDs

The number and percentage of subjects taking concomitant AEDs defined as AEDs taken concomitantly for at least one day in common with study medication will be summarized, separately, by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

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

#### 6.4.6 Non-AEDs taken prior to the Baseline Period

The number and percentage of subjects taking non-AEDs prior to the Baseline Period defined as medications with a start date prior to the date of informed consent, ie, prior to entry into the Baseline Period, will be summarized by WHODD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

#### 6.4.7 Non-AEDs taken during the Baseline Period

The number and percentage of subjects taking non-AEDs during the Baseline Period defined as medications with a start date on or after the date of informed consent and prior to the first dose of study medication, and medications with a start date prior to the date of informed consent and with a stop date on or after the start of the Baseline Period, will be summarized by WHODD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

#### 6.4.8 Concomitant Non-AEDs

The number and percentage of subjects taking concomitant non-AEDs defined as medications taken concomitantly for at least one day in common with study medication will be summarized by WHODD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

### 7 MEASUREMENTS OF TREATMENT COMPLIANCE

The total weight of used oral solution (mg) will be calculated as:

$$(\text{Sum of actual weight of used oral solution [g]} / 1.1\text{g/mL}) \times 10\text{mg/mL}$$

Note that the estimated weight of 1mL of oral solution is 1.1g, and the concentration is 10mg/mL.

Where:

$$\text{Actual weight of used oral solution (g)} = \text{Total weight of bottles (including adaptors and caps) at Dispensation} - \text{Total weight of bottles (including adaptors and caps) at Return}$$

The expected weight of used oral solution (mg) will be calculated as:

$$\text{Sum of daily oral solution (mg) for each day in the corresponding time period}$$

Where:

$$\text{Daily oral solution (mg)} = (\text{Morning dose [mg/kg]} + \text{Evening dose [mg/kg]}) \times \text{Baseline weight (kg)}$$

Total amount of tablets (mg) will be calculated as:



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$(100 \times [\text{number of 100 mg tablets dispensed} - \text{number of 100 mg tablets returned}] + 50 \times [\text{number of 50 mg tablets dispensed} - \text{number of 50 mg tablets returned}])$

Expected amount of tablets (mg) will be calculated as:

Sum of daily tablets (mg) for each day in the corresponding time period

Where:

Daily tablets (mg) = Morning dose (mg) + Evening dose (mg)

### Compliance

Compliance during a time period will be calculated using data from the respective time period only as follows:

$100 \times (\text{Total weight of used oral solution [mg]} + \text{Total amount of tablets used [mg]}) / (\text{expected weight of used oral solution [mg]} + \text{expected amount of tablets [mg]})$

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

Compliance will be summarized separately for the Titration Period, Maintenance Period, and entire Treatment Period for the SS. It will be presented using descriptive statistics and additionally using the categorization <75%, ≥75% to ≤125%, and >125%.

## **8 EFFICACY ANALYSES**

The primary and secondary efficacy variables will be measured using data obtained from the subject diary. Subjects or parents/caregivers will keep a diary to record the daily seizure activity from the beginning of the Baseline Period until the last visit, recording both seizure type, seizure frequency, and whether the seizures were a cluster.

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).

The assessment of efficacy is based on seizure frequency, and will be analyzed primarily for the FAS. All CIs presented will be 95% 2-sided CIs.

For subjects who prematurely discontinue from the study, last observation carried forward method as described in section 4.2 will be applied to obtain a seizure frequency estimate for the Maintenance Period.

All efficacy variables will be listed.

### **8.1 Statistical analysis of the primary efficacy variable**

#### **8.1.1 Derivations of primary efficacy variable**

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period. Seizure frequency per 28 days will be based on the number of days for which seizure information was provided during the specified time interval.

Seizure frequency per 28 days will be calculated as  $([\text{number of seizures over the specified time interval}] \text{ divided by } [\text{number of days in the interval}])$  multiplied by 28.

The partial-onset seizure frequency per 28 days will be calculated for both the Baseline Period and for the Maintenance Period, and the change from Baseline calculated.

If a seizure cluster is reported, the highest recorded daily seizure frequency during the Treatment Period for the seizure type associated with the report of a seizure cluster will be used as the imputed seizure frequency for the day on which the cluster occurred.

### **8.1.2 Primary analysis of the primary efficacy variable**

Seizure frequency will be analyzed using analysis of covariance (ANCOVA) with terms for treatment and center (pooled appropriately), on log-transformed seizure frequency using the transformation of  $\ln(X+1)$ , where X is the seizure frequency. Log transformed Baseline seizure frequency will be used as a covariate. Assumptions for the parametric model will be evaluated by diagnostic (eg, Shapiro-Wilk test for normality) and graphical methods such as residual plots, including normal probability plots, histograms, and plots of residuals versus Baseline covariate values and treatment. An assessment will be made with regards to the influence of individual observations (eg, extreme outliers) on the analysis. To the extent feasible, such potential influential observations will be identified prior to unblinding, and an assessment will be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If deemed that a non-parametric method is warranted, an ANCOVA model on rank of seizure frequency per 28 days with terms for treatment and center (pooled appropriately) will be employed as the primary analysis. Ranked seizure frequency per 28 days during the Baseline Period will be used as a covariate.

The seizure frequency between treatment and placebo will be compared using the least squares means (LSMs). The percent reduction over placebo will be estimated as  $100 \times (1 - \exp[\text{LSM}_{\text{LCM}} - \text{LSM}_{\text{placebo}}])$ . A 95% CI will also be calculated for the percent reduction over placebo.

Partial-onset seizure frequency per 28 days during the Baseline Period and during the Maintenance Period, and the change from Baseline will be summarized by treatment group. This summary will be repeated by treatment group and age group, using the levels defined in section 4.8.

### **8.1.3 Secondary analyses of the primary efficacy variable**

The primary analysis of the primary efficacy variable described in section 8.1.2 will be repeated for the PPS.

### **8.1.4 Supportive and sensitivity analyses of the primary efficacy variable**

The impact of missing data on the primary efficacy analysis will be evaluated by repeating the primary analysis of the primary efficacy variable detailed in section 8.1.2 on observed cases.

For subjects who prematurely discontinue from the study, only data recorded up to their ETV will be used to obtain a partial-onset seizure frequency estimate for the Maintenance Period.

## **8.2 Statistical analysis of the secondary efficacy variables**

The secondary efficacy variables will be summarized and/or analyzed for the FAS.

### **8.2.1 Change in partial-onset seizure frequency per 28 days from Baseline to entire Treatment Period**

The partial-onset seizure frequency per 28 days will be calculated for both the Baseline Period and for the entire Treatment Period, as detailed in section 8.1.1. The change from Baseline will also be calculated.

The change in partial-onset seizure frequency per 28 days from Baseline to the entire Treatment Period will be analyzed as detailed in section 8.1.2.

Partial-onset seizure frequency per 28 days during the Baseline Period and during the entire Treatment Period, and change from Baseline will be summarized by treatment group. This summary will be repeated by treatment group and age group, using the levels defined in section 4.8.

The change in seizure frequency per 28 days from Baseline to the Treatment Period, defined as the combined Titration and Maintenance Periods, will be summarized by treatment group (LCM or placebo) using descriptive statistics. Statistical testing will be performed using an ANCOVA model with terms for treatment and pooled site and baseline seizure frequency as a covariate.

The change in seizure frequency by period will also be summarized using descriptive statistics by treatment group and seizure type.

The change in seizure frequency by visit will also be summarized, based on observed analysis. For each visit during the Titration Period, the LCM treatment group will be compared to placebo in an exploratory onset of efficacy analysis. Statistical testing will be performed using an ANCOVA model with terms for treatment and pooled site and baseline seizure frequency as a covariate using data recorded at each individual Titration Period visit.

### **8.2.2 Proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in partial-onset seizure frequency from Baseline to end of Maintenance Period**

The secondary efficacy variable is the proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in partial-onset seizure frequency from Baseline to the end of Maintenance Period.

Percent reduction will be calculated as  $([\text{absolute reduction in partial-onset seizure frequency}] \div [\text{Baseline partial-onset seizure frequency}]) \times 100$ .

Absolute reduction in partial-onset seizure frequency is calculated as  $(\text{Baseline partial-onset seizure frequency}) - (\text{Maintenance Period partial-onset seizure frequency})$ .

The subject is considered a responder if the data shows a 50% or greater reduction in partial-onset seizure frequency from Baseline to end of Maintenance Period, otherwise the subject will be considered a non-responder.

This variable will be analyzed using a logistic regression model with terms for treatment and center to measure the association between the response variable and treatment after controlling for center. The odds ratio, 95% CI, and p-value associated with treatment will be presented.

The number and percentage of responders will be summarized by treatment group.

The response to treatment for each response level will also be summarized using descriptive statistics by treatment group and seizure type, with the seizure types presented as follows: simple partial seizures (IA), complex partial seizures (IB), partial seizures evolving to secondarily generalized (IC), generalized seizures (II), and unclassified epileptic seizures (III). This summary will be repeated by treatment group and age group, using the levels defined in section 4.8.

Only subjects who experienced the respective seizure type during the Baseline Period will be included in the analysis for that seizure type with only the seizure frequencies of that seizure type being used in the analysis. Subjects can be analyzed under multiple seizure types in these summaries. No statistical testing will be performed for these by seizure type summaries.

### **8.2.3 Proportion of subjects experiencing a $\geq 25\%$ to $< 50\%$ , 50% to 75%, or $> 75\%$ reduction in partial-onset seizure frequency from Baseline to end of Maintenance Period**

The proportion of subjects experiencing a  $\geq 25\%$  to  $< 50\%$ , 50% to 75%, or  $> 75\%$  reduction in partial-onset seizure frequency from Baseline to end of Maintenance Period will be summarized by treatment group.

Percent reduction will be calculated as defined in section 8.2.2.

The number and percentage of subjects in each of the categories will be summarized by treatment group.

### **8.2.4 Proportion of subjects experiencing a $\geq 25\%$ to $< 50\%$ , 50% to 75%, or $> 75\%$ reduction in partial-onset seizure frequency from Baseline to entire Treatment Period**

The secondary efficacy variable is the proportion of subjects experiencing a  $\geq 25\%$  to  $< 50\%$ , 50% to 75%, or  $> 75\%$  reduction in partial-onset seizure frequency from Baseline to the entire Treatment Period.

Percent reduction will be calculated as defined in section 8.2.2.

The number and percentage of subjects in each of the 3 categories will be summarized by treatment group.

Additionally, the proportion of subjects experiencing a  $\geq 25\%$  to  $< 50\%$ , 50% to 75%, or  $> 75\%$  reduction in partial-onset seizure frequency from Baseline to each post-Baseline scheduled visit during the entire Treatment Period will be determined.

Percent reduction will be calculated as defined in section 8.2.2, with absolute reduction in partial-onset seizure frequency calculated as (Baseline partial-onset seizure frequency) minus (Visit partial-onset seizure frequency).

Each subject will be categorized into 1 of the 3 reduction in partial-onset seizure groups ( $\geq 25\%$  to  $< 50\%$ , 50% to 75%, or  $> 75\%$ ), at each visit.

The number and percentage of subjects in each of the 3 categories will be summarized by treatment group for each post-Baseline visit.

### **8.2.5 Proportion of subjects experiencing no change in partial-onset seizure frequency from Baseline to entire Treatment Period**

The secondary efficacy variable is the proportion of subjects experiencing no change in partial-onset seizure frequency (between <25% reduction and <25% increase) from Baseline to the entire Treatment Period.

Percent reduction/increase will be calculated as defined in section 8.2.2.

Each subject will be categorized into 1 of the 2 partial-onset seizure frequency groups (between <25% reduction and <25% increase, or not between <25% reduction and <25% increase).

This variable will be analyzed using a logistic regression model with terms for treatment and center to measure the association between the response variable and treatment after controlling for center. The odds ratio, 95% CI, and p-value associated with treatment will be presented.

The number and percentage of subjects in each of the 2 categories will be summarized by treatment group.

### **8.2.6 Proportion of subjects experiencing an increase in partial-onset seizure frequency from Baseline to entire Treatment Period**

The secondary efficacy variable is the proportion of subjects experiencing an increase in partial-onset seizure frequency of  $\geq 25\%$  from Baseline to the entire Treatment Period.

Percent increase will be calculated as defined in section 8.2.2.

Each subject will be categorized in 1 of 2 increase in partial-onset seizure frequency groups ( $\geq 25\%$  or <25%).

This variable will be analyzed using a logistic regression model with terms for treatment and center to measure the association between the response variable and treatment after controlling for center. The odds ratio, 95% CI, and p-value associated with treatment will be presented.

The number and percentage of subjects in each of the 2 categories will be summarized by treatment group.

### **8.2.7 Change in partial-onset seizure frequency per 28 days from Baseline to the entire Treatment Period by seizure type**

The partial-onset seizure frequency per 28 days will be calculated for both the Baseline Period and for the entire Treatment Period, as detailed in section 8.1.1, by seizure type. The change from Baseline will also be calculated by seizure type.

The change in partial-onset seizure frequency per 28 days from Baseline to the entire Treatment Period will be analyzed as detailed in Section 8.1.2.

Partial-onset seizure frequency per 28 days during the Baseline Period and during the entire Treatment Period, and change from Baseline will be summarized by treatment group and seizure type.

In addition, descriptive statistics for change and percent change in seizure frequency per 28 days from Baseline to each post-Baseline visit during the entire Treatment Period will be presented by treatment group and seizure type. Partial-onset seizure frequency per 28 days will be presented

graphically at each visit by treatment group, and separately at each visit by seizure type and treatment group.

### **8.2.8 Proportion of seizure-free days during Maintenance Period**

For all subjects who enter the Maintenance Period, the proportion of seizure-free days during the Maintenance Period will be calculated.

The proportion of seizure-free days will be calculated as (days with number of seizures = 0 during the Maintenance Period) divided by (days with recorded data in the subject diary during the Maintenance Period), where “days with recorded data in the subject diary” excludes any days where “Not Done” is recorded.

Days with missing seizure diary information will be excluded from both the numerator and denominator for the seizure-free days calculation.

For all subjects who complete the Maintenance Period, the proportion of seizure-free days during the Maintenance Period will be calculated as described above, and summarized descriptively by treatment group.

Statistical testing for the proportion of seizure-free days during the Maintenance Period will be based on an ANCOVA model with terms for treatment and pooled site and a covariate of the proportion of seizure-free days during the Baseline Period. Only Subjects with efficacy data collected during the Maintenance Period will be included.

The proportion of seizure-free days during the Maintenance Period will also be summarized using descriptive statistics by treatment group and seizure type.

### **8.2.9 Proportion of subjects who achieved “seizure-free” status for subjects who completed the Maintenance Period**

A subject who completed the Maintenance Period will be defined as seizure-free if the subject did not report any seizures during the Maintenance Period, that is, there are no diary records during the Maintenance Period with either a count >0 or a reported seizure code with an unknown or missing seizure count.

Days with missing seizure diary data will be excluded from the determination of seizure free status as long as the percentage of days in the Maintenance Period with missing seizure diary data does not exceed 20%.

The number and percentage of subjects who achieved seizure free status during the Maintenance Period will be presented by treatment group.

## **8.3 Analysis of other efficacy variables**

The following efficacy variables will be summarized for the FAS.

### **8.3.1 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, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and a subject’s functional status. This will be assessed at Visit 8, or at ETV in case of early termination.

The number and percentage of subjects by Clinical Global Impression of Change value will be summarized for Visit 8 and Last Visit by treatment 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 for Visit 8 and Last Visit by treatment group. 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.

### **8.3.2 Caregiver’s Global Impression of Change**

The Caregiver’s Global Impression of Change is a 7-point categorical rating scale in which the caregiver assesses the subject’s change from Baseline in clinical status, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and a subject’s functional status. This will be assessed at Visit 8, or at ETV in case of early termination.

The number and percentage of subjects by Caregiver’s Global Impression of Change value will be summarized for Visit 8 and Last Visit by treatment 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 for Visit 8 and Last Visit by treatment group. 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.

### **8.3.3 PedsQL assessment**

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 administered only in countries where a translated version is available and will be completed at Visit 2 (Baseline), Visit 8, and at ETV in case of early termination.

PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales: Physical Functioning, Emotional Functioning, Social Functioning, and 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:  $100 - (\text{response} \times 25)$  in order to generate scores of 0, 25, 50, 75, and 100 where a higher value represents a better 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.

Calculated values and change from Baseline for the total scale score, psychosocial health score and each of the 4 scale scores will be summarized for each visit and Last Visit by treatment group. Subgroup summaries by age will be performed using the age groupings for which different questionnaires were entered:  $\geq 2$  to  $\leq 4$  years,  $\geq 5$  to  $\leq 7$  years,  $\geq 8$  to  $\leq 12$  years, and  $\geq 13$  to  $\leq 18$  years.

All PedsQL data will be listed.

#### **8.3.4 Concomitant medical procedures**

Subjects who had any concomitant medical procedures during the course of the study based on the Concomitant Medical Procedures eCRF will be listed. These will be attributed to the study periods based on the date of the procedure as defined in section 3.2.2. Additionally, subjects who had any procedures or surgeries prior to study entry based on the Procedure History eCRF will also be listed.

The number of concomitant medical procedures per subject will be summarized by treatment group for the Baseline Period and the entire Treatment Period, separately. The number of concomitant medical procedures per subject will be summarized using the categories 0, 1, 2, and 3 or more.

#### **8.3.5 Healthcare provider consultations**

Healthcare provider consultations not foreseen by the protocol will be attributed to study periods as defined in section 3.2.2 based on the date of consultation.

The number of healthcare provider consultations per subject during the Baseline Period and during the entire Treatment Period will be summarized, separately, by treatment group. 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 Baseline Period and during the Treatment Period, separately, will be summarized by type of provider (General Practitioner, Specialist Physician, Nurse, or Other) and treatment group. Percentages will be relative to the number of healthcare provider consultations during the Baseline Period and during the entire Treatment Period, respectively.

All healthcare provider consultations data will be listed.

#### **8.3.6 Hospital stays and emergency room visits**

Hospital stays and emergency room (ER) visits will be attributed to study periods as defined in section 3.2.2 based on admission date.

The number of hospital stays per subject during the Baseline Period and during the entire Treatment Period, separately, will be summarized by treatment group. 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 Baseline Period and for the duration of the entire Treatment Period, separately, by treatment group.



Duration of hospital stays 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 Baseline Period and the duration of the entire Treatment Period, separately, by treatment group.

An event logged on the Hospitalization/ER Visit eCRF module where ER is marked as the 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 Baseline Period and for the duration of the entire Treatment Period, will be presented, separately, by treatment group. 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 Baseline Period and the duration of the entire Treatment Period, separately, by treatment group.

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 hospital stays with a discharge date. 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. The durations of hospital stays will be summed within each of the study periods defined in section 3.2.2. Subjects with no hospital stays within a study period will have a duration of 0 days for that period. Should distinct records for hospital stays overlap, then the days during the overlap will only be counted once. Similarly, this also applies for the ER visits.

All hospitalization/ER data will be listed.

## **9 PHARMACOKINETICS**

### **9.1 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: arithmetic mean, SD, median, range, geometric mean, and geometric CV. The evaluations will be done based on separation by LCM maintenance dose level, and repeated by LCM maintenance dose level and age group.

Summarization of PK data relative to time after dose will be performed for the overall group and separated by AED therapy and possibly age groups.

### **9.2 Population pharmacokinetics**

A population PK modeling of the LCM concentration time data will be performed within the NONMEM software. The effects of age, body weight, AED therapy, and other covariates will be evaluated. Simulations will be undertaken for estimating dose adaptations leading to the same exposure as in adults.

The methods will be described in the Data Analysis Plan (DAP) and the results will be reported in a separate modeling report.

### 9.3 Exposure-response

A model-based approach will be used to describe the relationship between LCM and seizure counts data. The PK and pharmacodynamics (PD) data will be combined and exploratory analyses will be conducted to determine if a dose-response relationship can be demonstrated. Additional information will be documented separately in a DAP.

## 10 SAFETY ANALYSES

The following safety variables will be summarized for the SS.

### 10.1 Extent of exposure

All the summaries described below will also be presented for the FAS.

The overall duration of study medication exposure during each of the Titration Period, Maintenance Period and entire Treatment Period (defined in section 3.2.2) will be calculated, as follows:

Titration Period: date of last dose of study medication during the Titration Period minus the date of first dose of study medication plus 1.

Maintenance Period: date of last dose of study medication during the Maintenance Period minus the date of first dose of study medication during the Maintenance Period plus 1.

Entire Treatment Period: date of last dose of study medication during the entire Treatment Period minus the date of first dose of study medication plus 1.

The overall duration of study medication exposure will be summarized for each of the study periods defined above by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

In addition, the overall duration of study medication exposure will be summarized using the following categories for each of the study periods defined above by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8:

Titration Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks, and  $>4-\leq 6$  weeks.

Maintenance Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks, and  $>8-\leq 10$  weeks.

Entire Treatment Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks,  $>8-\leq 10$  weeks,  $>10-\leq 12$  weeks,  $>12-\leq 14$  weeks, and  $>14-\leq 16$  weeks.

The median total daily dose during the Titration Period, Maintenance Period, and entire Treatment Period will be summarized by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

In addition, for the Titration Period, the number of back titration steps for each subject (categorized as: 0, 1-3, 4-6, and  $\geq 7$ ), the number of subjects with a dose change together with the number of dose changes during the interval by dose back titration occurred (categorized as:  $< 2\text{mg/kg/day}$ ,  $\geq 2-\text{<}4\text{mg/kg/day}$ ,  $\geq 4-\text{<}6\text{mg/kg/day}$ ,  $\geq 6-\text{<}8\text{mg/kg/day}$ ,  $\geq 8-\text{<}10\text{mg/kg/day}$ ,  $\geq 10-\text{<}12\text{mg/kg/day}$ , and  $>12\text{mg/kg/day}$ ,  $<100\text{mg/day}$ ,  $\geq 100-\text{<}200\text{mg/day}$ ,  $\geq 200-\text{<}300\text{mg/day}$ ,  $\geq 300-\text{<}400\text{mg/day}$ , and  $\geq 400\text{mg/day}$ ), the number of up titration steps for each subject (categorized as: 0, 1-3, 4-6, and  $\geq 7$ ), and the number of subjects with a dose change together

with the number of dose changes during the interval by dose up titration occurred (categorized as: <2mg/kg/day, ≥2-<4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day, <100mg/day, ≥100-<200mg/day, ≥200-<300mg/day, ≥300-≤400mg/day, and >400mg/day), will be summarized by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

## 10.2 Adverse events

AEs will be tabulated by MedDRA SOC and MedDRA PT. 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 study medication administration. Treatment-emergent adverse events (TEAE) are defined as those events which start on or after the date of first study medication administration and within 30 days following the date of last study medication administration, or whose severity worsens within this time frame. Post-treatment AEs are defined as AEs which had an onset date after 30 days after the last study medication administration.

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

An overall summary of AEs 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 TEAE that led to permanent withdrawal of study medication, 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, 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 treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

The following summaries of AEs will be provided for each treatment group by MedDRA primary SOC and PT:

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

All three of these summaries will then be repeated by treatment group and age group, using the levels defined in section 4.8. In addition, all three of these summaries will be repeated including the site and subject number of all those subjects experiencing each TEAE and will be presented by treatment group.

The incidence of TEAEs during the Titration, Maintenance, Transition, Taper, and Safety Follow-Up Periods, separately, will also be presented for each treatment group by MedDRA primary SOC and PT.

The incidence of drug-related TEAEs by seriousness will be presented for each treatment group by MedDRA primary SOC and PT.

The incidence of TEAEs by dose at onset will be presented for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

The incidence of non-serious TEAEs occurring in at least 5% of subjects in any treatment group will be summarized for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group, using the levels defined in section 4.8.

Other significant AEs, defined in Appendix 12 (section 12.2), will be summarized for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and weight group, using the levels defined in section 4.8.

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

### 10.3 Clinical laboratory evaluations

Hematology, blood chemistry (including liver function tests), urinalysis, and endocrinology parameters are assessed throughout the study from Visit 1 (entry to study) to Visit 8, and at ETV in case of early termination, and may also be assessed at unscheduled visits. Laboratory parameters will also be assessed during the Transition Period (except endocrinology), Taper Period, and at the Safety Follow-Up Visit.

Urinalysis will be performed for subjects  $\geq 5$  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]), and change from Baseline will be summarized by treatment group 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 treatment group and gender.

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values which occur during the defined Treatment Period (see Section 3.2.2) at scheduled or unscheduled visits on or after the first study medication administration through to the end of the Treatment Period.

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

A serum pregnancy test will be performed on all females of childbearing potential at Visit 1 (entry to study), Visit 4, Visit 5, Visit 7, Visit 8, and at ETV in case of early termination. A serum pregnancy test will also be performed during the Taper Period, and at the Safety Follow-Up Visit, but only at the Safety Follow-Up Visit if blood is collected for other laboratory tests, otherwise a urine pregnancy test will be performed.

A urine pregnancy test will be performed at Visit 2 (Baseline), Visit 3, and Visit 6. A urine pregnancy test will also be performed at Visit 4 of the Transition Period, and at the Safety Follow-Up Visit, but only at the Safety Follow-Up Visit if a serum pregnancy test has not been performed.

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

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

### **10.4.1 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 from Visit 1 (entry to study) to Visit 8, and at ETV in case of early termination, and at unscheduled visits. Vital signs will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit.

Assessment of orthostatic changes 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.

Body weight will be assessed throughout the study from Visit 1 (entry to study) to Visit 8, and at ETV in case of early termination, and at unscheduled visits. Body weight will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit.

Height will be assessed at Visit 1 (entry to study), Visit 2 (Baseline), Visit 8, and at ETV in case of early termination. BMI will subsequently be calculated at these visits.

Head circumference will be assessed at Visit 1 (entry to study), Visit 8, and at ETV in case of early termination.

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

Orthostatic changes of SBP, DBP, and pulse rate will be summarized by treatment group for each visit and Last Visit.

Markedly abnormal (MA) values are defined as those MA values which occur during the defined Treatment Period (see Section 3.2.2) at scheduled or unscheduled visits on or after the first study medication administration through to the end of the Treatment Period.

The number and percentage of subjects with a MA value, MA low value, and MA high value, at each post-Baseline visit up to Visit 8, for which SBP, DBP, pulse rate, and body weight were

scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects with a value at each visit.

The abnormal vital sign criteria are defined as follows:

**Table 10–1: Vital Signs Abnormality Criteria**

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	4y - <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)	4y - <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)	4y - <12y	<50 >80
	12y - <17y	≤50 ≥105
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥105 and an increase from Baseline of ≥15
Respiratory Rate (breaths/minute)	4y - <12y	<15 >35
	≥12y	<10 >25
Temperature	All	>101 °F (38.3 °C)
Body Weight	4y - <17y	<3% or >97% of the normal body weight growth curve ranges <sup>a</sup> 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 = month, y = year. A month is defined as 30 days; a year is defined as 365.25 days.

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.

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 TEMA vital signs values will also be presented.

#### **10.4.2 Electrocardiograms**

Standard 12-lead ECGs (2 interpretable recordings [20 to 30 minutes apart]) will be performed throughout the study from Visit 1 (entry to study) to Visit 8, and at ETV in case of early termination. Standard 12-lead ECGs will also be performed at Visit 4 of the Transition Period, at week 18, 19, or 20 of the Taper Period, and at the Safety Follow-Up Visit.

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

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

Observed values of ECG results will be summarized for each visit and Last Visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits, and Last Visit by treatment group, and will be repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

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 treatment group at Visit 1 (entry to the study), Visit 2 (Baseline), and at each post-Baseline visit up to Visit 8, and Last Visit. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each time point based on the worst observed outcome across all abnormalities reported at that time point.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit, will also be provided by treatment group 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 (section 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 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). Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits)

and not meeting the same criteria during Baseline. All ECG parameter values will be listed for subjects meeting any abnormality criteria.

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

**Table 10–2: Electrocardiogram Abnormality Criteria**

Parameter	Age Range	Abnormality Criteria
QT interval (ms)	4y-<12y	≥500
	≥12y	≥500 or ≥60ms increase from Baseline
QTc(F) (ms)	4y-<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)	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)	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)	4y-<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)	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 30 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 study medication for each type of ECG abnormality.

### 10.4.3 Physical examination

#### 10.4.3.1 Complete physical examination

A complete physical examination will be performed at Visit 1 (entry to study), Visit 2 (Baseline), Visit 8, and at ETV in case of early termination. A complete physical examination will also be performed at Visit 4 of the Transition Period and at the Safety Follow-Up Visit.

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.



### **10.4.3.2 Brief physical examination**

A brief physical examination will be performed at Visit 3 to Visit 7. A brief physical examination will also be performed at Visit 1 to Visit 3 of the Transition Period, and at Week 18, 19, or 20 of the Taper Period, as appropriate.

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.

### **10.4.4 Neurological examination**

#### **10.4.4.1 Complete neurological examination**

A complete neurological examination will be performed at Visit 1 (entry to study), Visit 2 (Baseline), Visit 8, and at ETV in case of early termination. A complete neurological examination will also be performed at Visit 4 of the Transition Period and at the Safety Follow-Up Visit.

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.

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

Clinically significant neurological findings will be reported as AEs.

#### **10.4.4.2 Brief neurological examination**

A brief neurological examination will be performed at Visit 3 to Visit 7. A brief neurological examination will also be performed at Visit 1 to Visit 3 of the Transition Period, and at Week 18, 19, or 20 of the Taper Period, as appropriate.

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

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

Clinically significant neurological findings will be reported as AEs.

### **10.4.5 Vagus nerve stimulation**

Vagus nerve stimulation status is recorded throughout the study from Visit 1 (entry to study) to Visit 8, and at ETV in case of early termination, and at unscheduled visit, only for subjects with

an implanted VNS device. VNS status will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit only for those patients with an implanted VNS device.

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

#### 10.4.6 Tanner stage assessment

The investigator 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).

Tanner stage will be assessed at Visit 1 (entry to study) and at Visit 8, and at ETV in case of early termination.

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

#### 10.4.7 Achenbach Child Behavior Checklist

The Achenbach Child Behavior Checklist (CBCL) is completed at Visit 2 (Baseline), Visit 5 (End of Titration Period), Visit 8, and at ETV in case of early termination.

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 <17 years, the CBCL/6-18 will be used. For each subject, the same version (CBCL/1½-5 or CBCL/6-18) that is used at Visit 2 (Baseline) should be used at Visit 5, and Visit 8/ETV, and should be completed by the same parent/legal representative.

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 of sometimes true
- 2=very true or often true

The CBCL/1½-5 will be grouped according to syndrome scales in [Table 10-3](#) and the CBCL/6-18 will be grouped according to empirically based syndrome scales in [Table 10-4](#).

**Table 10-3: 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

**Table 10–3: CBCL/1½-5**

Syndrome scale	Questions
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 10–4: 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, by treatment group.

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, by treatment group.

#### 10.4.8 Assessment of suicidality

Suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). The scale will be used for Screening as well as to assess suicide ideation and behavior that may occur during the study. All subjects who are  $\geq 6$  years of age will complete the Baseline/Screening version of the C-SSRS at Visit 1 and will complete the Since Last Visit version at subsequent visits. If a subject becomes 6 years of age during the study, the Already Enrolled version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and use the Since Last Visit version at subsequent visits.

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

The C-SSRS assessment is completed throughout the study from Visit 1 (entry to study) to Visit 8, and at ETV in case of early termination, and at unscheduled visits. The C-SSRS assessment is also completed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit.

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

#### 10.4.9 BRIEF-P and BRIEF assessment

The BRIEF-P/BRIEF assessments are completed at Visit 2 (Baseline), Visit 8, and at ETV in case of early termination.

The BRIEF-P and BRIEF are validated tools that will be used for the evaluation of subjects  $\geq 2$  to  $< 5$  years of age, and  $\geq 5$  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 8/ETV.

##### 10.4.9.1 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 10-5](#).

**Table 10-5: 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
<b>Inhibitory self-control</b>	<b>All from {Inhibit and Emotional Control}</b>
<b>Flexibility</b>	<b>All from {Shift and Emotional Control}</b>

**Table 10–5: BRIEF-P questionnaire scoring**

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

GEC=Global Executive Composite

Standardized T-scores are determined from each subject’s raw GEC, inhibitory self-control, flexibility, emergent metacognition, 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 3 indexed scores and GEC for the BRIEF-P questionnaire will be summarized at Visit 8, and Last Visit, by treatment group.

All BRIEF-P assessment data will be listed.

**10.4.9.2 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 10–6](#).

**Table 10–6: 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
<b>Behavioral Regulation Index (BRI)</b>	<b>All from {Inhibit, Shift, and Emotional Control}</b>
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

**Table 10–6: BRIEF questionnaire scoring**

Scale/Index	Questions
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.

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 at Visit 8, and Last Visit, by treatment group.

All BRIEF assessment data will be listed.

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## 11 REFERENCES

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## 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 >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 <sup>9</sup> /L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0
Lymphocytes Absolute	<2y	10 <sup>9</sup> /L	<1.0 >9.8	G/L	<1.0 >9.8
	2y - <6y	10 <sup>9</sup> /L	<0.7 >6.9	G/L	<0.7 >6.9
	≥6y	10 <sup>9</sup> /L	<0.6 >5.0	G/L	<0.6 >5.0
Basophils	>1m	%	≥5.0	%	≥5.0
Basophils Absolute	>1m	10 <sup>9</sup> /L	≥0.4	G/L	≥0.4
Eosinophils	>1m	%	≥10	%	≥10
Eosinophils Absolute	>1m	10 <sup>9</sup> /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 <sup>9</sup> /L	≥2.0	G/L	≥2.0
Neutrophils Absolute	>1m	10 <sup>9</sup> /L	<1.5	G/L	<1.5
Platelets	>1m	10 <sup>9</sup> /L	≤100 ≥600	G/L	≤100 ≥600
RBC/ Erythrocytes	<2y	10 <sup>12</sup> /L	<3.0	T/L	<3.0
	≥2y	10 <sup>12</sup> /L	<3.5	T/L	<3.5

Abbreviations: m =month, y = year. A month is defined as 30 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 ≥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
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

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

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
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 >8.4	g/L	<26 >84
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
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 <sup>a b</sup>	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

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

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

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

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

<sup>a</sup> Schwartz equation (patients <12): Cr Cl ml/min = [Height (cm) \* 0.55] / serum creatinine

<sup>b</sup> Cockcroft equation (patients >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 adverse events

<b>MedDRA Preferred Term</b>
<b>HEPATOTOXICITY RELATED TERMS</b>
Hepatitis toxic
Hepatotoxicity
<b>CARDIAC AND ECG RELATED TERMS</b>
Atrioventricular block third degree
Atrioventricular block second degree
Bradycardia
Bradycardia
Cardiac pacemaker insertion
Atrial fibrillation
Atrial flutter
Sinus bradycardia
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased
Sick sinus syndrome
<b>SUICIDALITY RELATED TERMS</b>
Completed suicide
Depression suicidal
Suicidal behavior
Suicidal ideation
Suicide attempt
Intentional self-injury
Self injurious behavior
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
<b>ADDITIONAL TERMS</b>
Loss of consciousness
Syncope

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## **13 AMENDMENTS TO THE STATISTICAL ANALYSIS PLAN**

### **13.1 Amendment 1**

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

#### **Global change**

The following global change was made throughout the SAP:

- Last Value has been changed to Last Visit
- WHO-DD has been changed to WHODD
- For AEs, primary SOC is now written as MedDRA primary SOC
- References to Appendix 12 (Table 12.2) have been changed to reference Appendix 12 (section 12.2)

#### **Specific changes**

##### **Change #1**

Added ANCOVA – analysis of covariance to the list of abbreviations

Added MA – markedly abnormal to the list of abbreviations.

##### **Change #2**

The statistical analysis plan signature page has been removed and the new e-signature page has been included in its place.

##### **Change #3**

#### **Section 2.2.1.3 Other efficacy variables**

Other efficacy variables to be examined include:

- Clinical Global Impression of Change at the end of the Maintenance Period
- Caregiver's Global Impression of Change at the end of the Maintenance Period
- Quality of life assessments (PedsQL)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)

#### **Has been changed to:**

Other efficacy variables to be examined include:

- Clinical Global Impression of Change at the end of the Maintenance Period
- Caregiver's Global Impression of Change at the end of the Maintenance Period
- Quality of life assessments (PedsQL)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol)

## Change #4

### Section 2.3 Study design and conduct

Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will enter a 4-week blinded Transition Period. Subjects randomized to LCM will maintain their Maintenance Period dose during the Transition Period. Subjects randomized to placebo will transition to LCM in a double-blind fashion in accordance with the schedule provided in Table 3-4.

The blinded Taper Period (2 to 4 weeks, depending on dose level achieved) is for subjects who will not be entering the open-label extension study (EP0034) for any of the following reasons:

- Subject does not complete the Titration Period, the Maintenance Period, or the Transition Period
- Subject does not choose to enroll in the open-label extension study (EP0034) after completing the Maintenance Period or the Transition Period

Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

The dosing of study medication for the Taper Period is provided in Table 3-5.

There will be a 30-day Safety Follow-Up Period for subjects not entering the open-label extension study (EP0034).

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

Each subject's total duration of study medication administration is up to 24 weeks. The total study duration can be up to 36 weeks, including the 30-day safety Follow-Up Period.

Detailed tabular schedules of study procedures are provided in Table 2-1, Table 2-2, and Table 2-3.

**Table 2-1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, Early Termination Visit, and Unscheduled Visits)**

Assessments	Baseline Period (8 weeks)			Treatment Period (16 weeks)										ETV	Unscheduled Visit <sup>c</sup>	
				Titration Period (6 weeks)						Maintenance Period (10 weeks)						
Visit	V1 <sup>a</sup>	T1	V2	T2	V3	T3	V4	T4	V5	V6	T5	V7	T6	V8 <sup>b</sup>		
Week in study	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16		
Informed consent	X															
Inclusion/exclusion criteria	X	X	X													
Medical history	X															
Seizure history	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VNS assessment <sup>d</sup>	X		X		X		X		X	X		X		X	X	X
Physical examination (complete)	X		X											X	X	
Physical examination (brief)					X		X		X	X		X				
Tanner Stage <sup>e</sup>	X													X	X	
Vital signs (BP and pulse rate, including orthostatic assessments)	X		X		X		X		X	X		X		X	X	X
Body weight	X		X		X		X		X	X		X		X	X	X
Height	X		X											X	X	
Head circumference	X													X	X	
Neurological examination (complete)	X		X											X	X	



**Table 2-1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, Early Termination Visit, and Unscheduled Visits)**

Assessments	Baseline Period (8 weeks)			Treatment Period (16 weeks)											ETV	Unscheduled Visit <sup>c</sup>
	Visit	Titration Period (6 weeks)						Maintenance Period (10 weeks)								
Week in study	V1 <sup>a</sup>	T1	V2	T2	V3	T3	V4	T4	V5	V6	T5	V7	T6	V8 <sup>b</sup>		
Neurological examination (brief)					X		X		X	X		X				
ECG (12-lead) <sup>f</sup>	X		X		X		X		X	X		X		X	X	
Clinical chemistry/hematology	X		X				X		X			X		X	X	
Endocrinology			X											X	X	
Urinalysis <sup>g</sup>	X		X				X		X			X		X	X	
Serum pregnancy test <sup>h</sup>	X						X		X			X		X	X	
Urine pregnancy test <sup>h</sup>			X		X					X						
Concomitant AED plasma concentrations <sup>i</sup>	X								X					X	X	
LCM plasma concentration <sup>i</sup>	X								X					X	X	
C-SSRS <sup>j</sup>	X		X		X		X		X	X		X		X	X	X
Clinical Global Impression of Change														X	X	
Caregiver's Global Impression of Change														X	X	
Achenbach CBCL <sup>k</sup>			X						X					X	X	
BRIEF-P/BRIEF <sup>l</sup>			X											X	X	
PedsQL <sup>m</sup>			X											X	X	
Contact IXRS	X		X		X		X		X	X		X		X	X	

**Table 2-1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, Early Termination Visit, and Unscheduled Visits)**

Assessments	Baseline Period (8 weeks)			Treatment Period (16 weeks)											ETV	Unscheduled Visit <sup>c</sup>
	Visit	Titration Period (6 weeks)						Maintenance Period (10 weeks)								
Visit	V1 <sup>a</sup>	T1	V2	T2	V3	T3	V4	T4	V5	V6	T5	V7	T6	V8 <sup>b</sup>		
Week in study	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16		
Randomization <sup>n</sup>			X													
Dispense study medication			X <sup>l</sup>		X		X		X	X		X		X	X	
Study medication return					X		X		X	X		X		X	X	
Subject diary <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X		X
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments of epilepsy surgery/VNS	X															
Health care resource use	X		X		X		X		X	X		X		X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; T=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

Note: For all visits shown in Table 2-1 a time window of ±2 days relative to Visit 2 (Baseline Period) is applicable. During the Treatment Period, each visit should occur at the end of the week indicated in accordance with this time window.

<sup>a</sup>Visit 1 (V1) may occur over more than 1 day; however, all results of Visit 1 assessments should be available before T1.

<sup>b</sup>At the end of Visit 8, subjects who complete the Maintenance Period may be eligible to participate in an open-label extension study (EP0034). Subjects who plan to enroll in the open-label extension study will proceed to a 4-week blinded Transition Period. Subjects who choose not to enter the open-label extension study or who do not complete the Maintenance Period will proceed to a blinded Taper Period (2 to 4 weeks, depending on dose level achieved). Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

<sup>c</sup>If an Unscheduled Visit is needed (eg, due to AE), then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion. The C-SSRS will be completed at an Unscheduled Visit only if the visit is related to an AE.

<sup>d</sup>Only applicable for subjects with an implanted VNS device.

<sup>e</sup>The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study.

<sup>f</sup>A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment. The subject should rest in the supine position for approximately 5 minutes before the recordings and during the recordings, if possible. The recordings should be made 20 to 30 minutes apart.

<sup>g</sup>Urinalysis will be performed for subjects  $\geq 5$  years of age only.

<sup>h</sup>Pregnancy tests will be performed for female subjects of childbearing potential only.

<sup>i</sup>Blood samples for analysis of concomitant AED plasma concentrations and/or LCM will be drawn along with clinical chemistry, hematology, and endocrinology samples, as applicable.

<sup>j</sup>The C-SSRS will be completed for all subjects  $\geq 6$  years of age. The C-SSRS will be completed at an Unscheduled Visit only if the visit related to an AE.

<sup>k</sup>The Achenbach CBCL: CBCL/1½ -5 for children 18 months to 5 years and 11 months of age, and CBCL/6-18 for children  $\geq 6$  years to  $< 17$  years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each subject, the same version of the scale that was completed at Visit 2 (CBCL/1½ -5 or CBCL/6-18) should be maintained for the duration of the study and should be completed by the same parent/legal representative. The Achenbach CBCL will be used only in countries where a translated version is available.

<sup>l</sup>The BRIEF-P should be used for subjects who are  $\geq 2$  years to  $< 5$  years of age at Visit 2, and the BRIEF should be used for subjects who are  $\geq 5$  years of age at Visit 2. The same version of the scale that was completed at Visit 2 (BRIEF-P or BRIEF) should be maintained for each subject for the duration of the study. The BRIEF-P and BRIEF will be used only in countries where a translated version is available.

<sup>m</sup>The version of the PedsQL used at Visit 2 should be consistent with the subject's age at Visit 2 and should be maintained for each subject for the duration of the study. The PedsQL will be used only in countries where a translated version is available.

<sup>n</sup>At the end of Visit 2, subjects should take the first dose of study medication in the clinic.

<sup>o</sup>The subject diary will be dispensed at Visit 1. At all subsequent visits, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis.

**Table 2-2: Schedule of study assessments (Transition Period)**

Assessment	Transition Period (4 weeks) <sup>a</sup>			
	TV1	TV2	TV3	TV4
Week in study	17 <sup>a</sup>	18	19	20
Concomitant medications	X	X	X	X
Concomitant AEDs	X	X	X	X
VNS assessments <sup>b</sup>	X	X	X	X
Physical examination (complete)				X
Physical examination (brief)	X	X	X	
Vital signs (BP and pulse rate, including orthostatic assessment)	X	X	X	X
Body weight	X	X	X	X
Neurological examination (complete)				X
Neurological examination (brief)	X	X	X	
12-lead ECG <sup>c</sup>				X
Clinical chemistry/hematology				X
Urinalysis <sup>d</sup>				X
Urine pregnancy test <sup>e</sup>				X
Concomitant AED plasma <sup>f</sup> concentrations				X
LCM plasma concentration <sup>f</sup>				X
C-SSRS <sup>g</sup>	X	X	X	X
Contact IXRS	X	X	X	X
Dispense study medication	X	X	X	
Study medication return	X	X	X	X
Subject diary <sup>h</sup>	X	X	X	X
Withdrawal criteria	X	X	X	X
AE reporting	X	X	X	X
Health care resource use	X	X	X	X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IXRS=interactive voice/web response system; LCM=lacosamide; TV=Transition Visit; VNS=vagus nerve stimulation

Note: For all visits shown in , a window of ±2 days relative to Visit 2 (Baseline Period) is applicable. Each visit should occur at the end of the week indicated in accordance with this time window.

<sup>a</sup>At the end of Visit 8, (Maintenance Period), subjects may be eligible to participate in an open-label extension study (EP0034). Subjects who plan to enroll in the open-label extension study will enter a 4-week blinded Transition

Period.

<sup>b</sup>Only applicable for subjects with an implanted VNS device.

<sup>c</sup>A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment.

The subject should rest in the supine position for approximately 5 minutes before the ECG recording and during the recordings if possible. The recordings should be made 20 to 30 minutes apart.

<sup>d</sup>Urinalysis will be performed for subjects  $\geq 5$  years of age only.

<sup>e</sup>Pregnancy tests will be performed for female subjects of childbearing potential only.

<sup>f</sup>Blood samples for analysis of concomitant AED plasma concentrations and/or LCM will be drawn along with clinical chemistry, hematology, and endocrinology samples, as applicable.

<sup>g</sup>The C-SSRS will be completed for all subjects  $\geq 6$  years of age.

<sup>h</sup>The subject diary will be returned at TV4. At all other visits, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis.

**Table 2-3: Schedule of study assessments (Taper Period and Safety Follow-Up Period)**

Assessment	Taper Period <sup>a</sup> (2 to 4 weeks)		Safety Follow-Up Period <sup>b</sup> (30 days)		
	Visit	T7 <sup>c</sup>	Taper Visit <sup>d</sup>	Safety Follow-Up Visit	Safety Follow-Up Telephone Contact
<b>Week in study</b>	<b>17</b>	<b>18, 19, or 20</b>	<b>20, 21, or 22</b>	<b>22, 23, or 24</b>	
Concomitant medications	X	X	X	X	
Concomitant AEDs	X	X	X	X	
VNS assessment <sup>e</sup>		X	X		
Physical examination (brief)		X			
Physical examination (complete)				X	
Vital signs (BP and pulse rate, including orthostatic assessment)		X	X		
Body weight		X	X		
Neurological examination (brief)		X			
Neurological examination (complete)				X	
ECG (12-lead) <sup>g</sup>		X	X <sup>g</sup>		
Clinical chemistry/hematology		X	X <sup>g</sup>		
Endocrinology		X	X <sup>g</sup>		
Urinalysis <sup>h</sup>		X	X		
Serum pregnancy test		X	X <sup>i</sup>		
Urine pregnancy test			X <sup>i</sup>		
C-SSRS <sup>j</sup>		X	X		
Contact IXRS		X			

Study medication return		X		
Subject diary <sup>k</sup>	X	X		
Withdrawal criteria	X	X		
AE reporting	X	X	X	X
Health care resource use		X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IXRS=interactive voice/web response system; LCM=lacosamide; T=Telephone Contact; VNS=vagus nerve stimulation

Note: The study week numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study week numbers provided do not apply to subjects who enter the Taper Period at other times.

<sup>a</sup>A blinded Taper Period (2 to 4 weeks, depending on dose achieved) will be required for subjects who discontinue study medication prematurely and for subjects who complete the Maintenance Period but choose not to enter the open-label extension study (EP0034). Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and or parent/legal representative.

<sup>b</sup>The Safety Follow-Up Visit will occur 2 weeks ( $\pm 2$  days) after the final dose of study medication. The Safety Follow-Up Telephone Contact will occur 30 days ( $-1/+3$  days) after the final dose of study medication.

<sup>c</sup>A telephone contact (T7) will be conducted at the end of the first week of the Taper Period.

<sup>d</sup>Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Week 18, Week 19, or Week 20, depending on dose level achieved; see of the Protocol). A time window of  $\pm 2$  days relative to Visit 2 (Baseline Period) is applicable.

<sup>e</sup>Only applicable for subjects with an implanted VNS device.

<sup>f</sup>A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment. The subject should rest in the supine position for approximately 5 minutes before the recording and during the recordings, if possible. The recordings should be made 20 to 30 minutes apart.

<sup>g</sup>The assessment will only be required for subjects with an abnormal value (clinical chemistry, hematology, or endocrinology) or reading (ECG) at the previous clinic visit.

<sup>h</sup>Urinalysis will be performed for subjects  $\geq 5$  years of age only.

<sup>i</sup>Pregnancy tests will be performed for female subjects of childbearing potential only. A serum pregnancy test will be performed at the Safety Follow-Up Visit only if blood is collected for other laboratory tests. If no blood is collected for other assessments, then a urine pregnancy test will be performed.

<sup>j</sup>The C-SSRS will be completed for all subjects  $\geq 6$  years of age.

<sup>k</sup>At T7, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis. The subject diary will be returned at the Taper Visit.

### Has been changed to:

Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will enter a 4-week blinded Transition Period. Subjects randomized to LCM will maintain their Maintenance Period dose during the Transition Period. Subjects randomized to placebo will transition to LCM in a double-blind fashion in accordance with the schedule provided in Table 7-4 of the protocol.

The blinded Taper Period (2 to 4 weeks, depending on dose level achieved) is for subjects who will not be entering the open-label extension study (EP0034) for any of the following reasons:

- Subject does not complete the Titration Period, the Maintenance Period, or the Transition Period
- Subject does not choose to enroll in the open-label extension study (EP0034) after completing the Maintenance Period or the Transition Period

Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

The dosing of study medication for the Taper Period is provided in Table 7-5 of the protocol .

There will be a 30-day Safety Follow-Up Period for subjects not entering the open-label extension study (EP0034).

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

Each subject's total duration of study medication administration is up to 24 weeks. The total study duration can be up to 36 weeks, including the 30-day safety Follow-Up Period.

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

### **Change #5**

#### **Section 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 9.1.3. All tables and listings will use Courier New font size 9.

#### **Has been changed to:**

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.3. All tables and listings will use Courier New font size 9.

### **Change #6**

#### **Section 3.2.2 Study periods**

##### Maintenance Period

On or after the start of the Maintenance Period (Visit 6) and prior to or on the end date of the Maintenance Period (Visit 8) for subjects who complete the Maintenance Period, or on or after the date of first dose of study medication and prior to or on the date of the ETV for subjects who discontinue during the Maintenance Period. If a subject does not have a Visit 8/ETV, then either the date of the last scheduled or unscheduled visit during the Maintenance Period or the date of last known dose of study medication during the Maintenance Period, whichever is later, will define the end date of the Maintenance Period.

#### **Has been changed to:**

##### Maintenance Period

The day after the end of the Titration Period (Visit 5) and prior to or on the end date of the Maintenance Period (Visit 8) for subjects who complete the Maintenance Period, or on or after the date of first dose of study medication and prior to or on the date of the ETV for subjects who discontinue during the Maintenance Period. If a subject does not have a Visit 8/ETV, then either the date of the last scheduled or unscheduled visit during the Maintenance Period or the date of last known dose of study medication during the Maintenance Period, whichever is later, will define the end date of the Maintenance Period.

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## Change #7

### Section 3.2.4 Last Value on study medication

The Last Value on study medication for all assessments is the last available result obtained after first dose of study medication and prior to or on the last dose of study medication. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each vital sign, ECG, and laboratory parameter.

#### Has been changed to:

### Section 3.2.4 Last Visit

The Last Visit for all assessments 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.

## Change #8

### Section 3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary efficacy outcome or key safety 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 blinded Data Evaluation Meeting (DEM) prior to unblinding of the database.

#### Has been changed to:

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary efficacy outcome or key safety 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 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 blinded Data Evaluation Meetings (DEMs) prior to unblinding of the database. A list of subjects with important protocol deviations will be agreed upon during the DEMs and will be documented in the DEM minutes.

### **Change #9**

#### **Section 3.5 Analysis sets**

The analysis sets defined for this study are the Safety Set (SS), Full Analysis Set (FAS), Per Protocol Set (PPS), and PK Set (PK-PPS).

#### **Has been changed to:**

The analysis sets defined for this study are the Safety Set (SS), Full Analysis Set (FAS), Per Protocol Set (PPS), and Pharmacokinetic Per Protocol Set (PK-PPS).

### **Change #10**

#### **Section 3.5.4 Pharmacokinetic Set**

All subjects from the SS with valid LCM plasma concentration data will be included in the PK-PPS.

#### **Has been changed to:**

#### **Section 3.5.4 Pharmacokinetic Per Protocol Set**

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

### **Change #11**

#### **Section 3.6 Treatment assignment and treatment groups**

It is expected that subjects will receive treatment as randomized. Thus, treatment assignment for the FAS and the SS will be according to randomization. However, if after unblinding it is determined that the subjects received treatment other than what they were randomized to receive, the safety analyses will be conducted using treatment assignments according to the actual treatment received (SS-as treated).

The recommended dosing schedule for LCM or matching placebo during the Titration Period is detailed in [Table 3-1](#). The dosing of LCM or matching placebo with flexibility based on tolerability during the Titration Period is detailed in [Table 3-2](#). The required LCM or matching placebo dose for at least the final 3 days of Week 6 is detailed in [Table 3-3](#). Similarly, Transition Period LCM dosing schedule for subjects randomized to placebo, and Taper Period dosing of LCM or matching placebo, are detailed in [Table 3-4](#) and [Table 3-5](#), respectively.

**Table 3-1: Recommended dosing schedule for LCM (or matching placebo) during the Titration Period**

Body weight category (formulation)	Target LCM (or matching placebo) doses for the Titration Period					
	Week 1 <sup>a</sup>	Week 2	Week 3	Week 4	Week 5	Week 6
<30kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/day	12mg/kg/day
≥30kg to <50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	8mg/kg/day	8mg/kg/day
≥50kg (tablets)	100mg/day	200mg/day	300mg/day	400mg/day	400mg/day	400mg/day

LCM=lacosamide

Note: Subjects may not receive doses higher than LCM 12mg/kg/day (body weight <30kg), LCM 8mg/kg/day (body weight ≥30kg to <50kg), or LCM 400mg/day (body weight ≥50kg), or matching placebo.

<sup>a</sup>All subjects are required to complete Week 1 study medication dosing before dosing flexibility is allowed based on tolerability. Subjects who are unable to complete the Titration Period or subjects who will not be able to attain at least the minimum Maintenance Period target dose, should be withdrawn and enter the Taper Period.

**Table 3-2: Dosing of LCM (or matching placebo) with flexibility based on tolerability during the Titration Period**

Body weight category (formulation)	Target LCM (or matching placebo) dose increase/week <sup>a</sup> (titration)	LCM (or matching placebo) dose decrease per back titration step		Subsequent LCM (or matching placebo) dose increase <sup>b</sup> (dose increase after back titration step)	
		Min	Max	Min	Max
<30kg (oral solution)	2mg/kg/day	1mg/kg/day	2mg/kg/day	1mg/kg/day	2mg/kg/day
≥30kg to <50kg (oral solution)					
≥50kg (tablets)	100mg/day	50mg/day	100mg/day	50mg/day	100mg/day

LCM=lacosamide; Max=maximum; Min=minimum

Note: Asymmetrical dosing with no more than 50mg difference between morning and evening doses will be allowed for subjects taking tablets who require back titration in a 50mg increment (ie, only 50mg and 100mg tablets are available)

<sup>a</sup> Titration step to achieve a dose not previously administered

<sup>b</sup> Titration step subsequent to a back titration

**Table 3-3: Required LCM (or matching placebo) dose for at least the final 3 days of Week 6**

Body weight category (formulation)	LCM (or matching placebo) dose for at least the final 3 days of Week 6	
	Min	Max
<30kg (oral solution)	8mg/kg/day	12mg/kg/day
≥30kg to <50kg (oral solution)	6mg/kg/day	8mg/kg/day
≥50kg (tablets)	300mg/day	400mg/day

LCM=lacosamide; Max=maximum; Min=minimum

**Table 3-4: Transition Period LCM dosing schedule for subjects randomized to placebo**

Body weight category (formulation)	LCM doses for the Transition Period			
	Week 17	Week 18	Week 19	Week 20
<30kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day
≥30kg to <50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	6mg/kg/day
≥50kg (tablets)	100mg/day	200mg/day	300mg/day	300mg/day

LCM=lacosamide

**Table 3-5: Taper Period dosing of LCM (or matching placebo)**

LCM (or matching placebo) dose achieved	LCM (or matching placebo) doses for the Taper Period			
	Week 17	Week 18	Week 19	Week 20
11 or 12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9 or 10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7 or 8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day
5 or 6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day	NA
3 or 4mg/kg/day	2mg/kg/day	2mg/kg/day	NA	NA
2mg/kg/day	NA	NA	NA	NA
350 or 400mg/day	300mg/day	200mg/day	100mg/day	100mg/day
250 or 300 mg/day	200mg/day	100mg/day	100mg/day	NA
150 or 200mg/day	100mg/day	100mg/day	NA	NA
100mg/day	NA	NA	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)

Note: The oral solution is dosed as mg/kg/day and tablets are dosed as mg/day.

Note: Subjects not requiring taper will enter directly into the Safety Follow-Up Period and not attend any Taper Period visits.

Note: The study week numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study week numbers provided do not apply to subjects who enter the Taper Period at other times.

**Has been changed to:**

It is expected that subjects will receive treatment as randomized. Thus, treatment assignment for the FAS and the SS will be according to randomization. However, if after unblinding it is determined that the subjects received treatment other than what they were randomized to receive, the safety analyses will be conducted using treatment assignments according to the actual treatment received (SS-as treated).

All subjects treated in this study receive LCM at doses ranging from 8mg/kg/day to 12mg/kg/day (oral solution) for subjects weighing <30kg, 6mg/kg/day to 8mg/kg/day (oral solution) for

subjects weighing  $\geq 30$ kg to  $< 50$ kg, 300mg/day to 400mg/day (tablets) for subjects weighing  $\geq 50$ kg, or matching placebo. The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study. Summaries will be presented based on treatment group; Placebo and LCM, and will generally not be differentiated by LCM dose. Where appropriate, LCM dose will be presented in subject data listings.

## Change #12

### Section 4.2 Handling of dropouts or missing data

For subjects who discontinue prior to the Maintenance Period, all available seizure frequency data will be carried forward from the Titration Period for the Maintenance Period analysis. For subjects who prematurely discontinue during the Maintenance Period, all available seizure frequency data in the Maintenance Period will be carried forward for the entire Maintenance Period.

Subjects who discontinue prior to any efficacy data collection will not be included in the analysis (ie, data will not be carried forward from Baseline). The imputation for the seizure frequency data will not carry forward into the Transition and Taper Periods.

No imputation of missing values associated with an individual date or visit is planned for the primary safety analysis, with the exception of partial date information for AEs and concomitant medications in order to determine whether they are treatment-emergent.

Adverse events with an incomplete onset date will be classified as a treatment-emergent adverse event (TEAE) if the month and year of onset (when only the month and year are specified) is the same as the month and years of the first dose of study medication, or the year of onset (when only year is specified) is the same as the year of first dose of study medication.

#### Has been changed to:

### Section 4.2 Handling of dropouts or missing data

#### Section 4.2.1 Missing data

For subjects who discontinue prior to the Maintenance Period, all available seizure frequency data will be carried forward from the Titration Period for the Maintenance Period analysis. For subjects who prematurely discontinue during the Maintenance Period, all available seizure frequency data in the Maintenance Period will be carried forward for the entire Maintenance Period.

Subjects who discontinue prior to any efficacy data collection will not be included in the analysis (ie, data will not be carried forward from Baseline). The imputation for the seizure frequency data will not carry forward into the Transition and Taper Periods.

No imputation of missing values associated with an individual date or visit is planned for the primary safety analysis, with the exception of partial date information for AEs and concomitant medications in order to determine whether the AEs are treatment-emergent or the medications are concomitant.

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to study medication per the investigator will be assumed to be related. Incomplete or missing dates for events will be handled as described in section 3.2.2.

#### **Section 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 study medication 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 study medication. 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 study medication 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 study medication. 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 study medication.

However, if the study termination year and year for the date which is 28 days after last intake of study medication are greater than the event/concomitant medication year, the day and month are to be set to December 31st.

#### **Section 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 study medication will be considered as concomitant medication. Medications with missing start date whose stop date is prior to first intake of study medication will not be considered concomitant.

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

#### **Section 4.2.4 Incomplete dates for the last administration of study medication**

For purposes of imputing missing components of partially reported dates for the last administration of study medication, the algorithms listed below will be followed. Stop dates of study medication 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.

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.

#### **Section 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. If more than 10% of the diary entries are missing for a specific subject and time interval, then that subject will not be considered for the calculation of seizure frequency or seizure-free days during the time interval.

#### **Section 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 study medication
- 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.

### **Change #13**

#### **Section 4.3 Interim analyses and data monitoring**

To ensure subject safety, interim reviews of the safety data will be performed using an Independent Data monitoring Committee (IDMC). Serious adverse events and other significant events (detailed in Appendix 12 (Table 12.2)) are monitored and will be triaged by the medical monitor and UCB Drug Safety in real time.

**Has been changed to:**

No informal interim analysis for determination of efficacy is planned for this study. To ensure subject safety, interim reviews of the safety data will be performed using an Independent Data monitoring Committee (IDMC). Serious adverse events and other significant events (detailed in Appendix 12 (Table 12.2)) are monitored and will be triaged by the medical monitor and UCB Drug Safety in real time.

**Change #14**

**Section 4.6 Use of an efficacy subset of subjects**

The PPS will be used to evaluate subjects who have efficacy data during the entire treatment period and have no important protocol deviations related to efficacy. This analysis set will provide additional information on the analysis of the primary efficacy variable and will describe findings in a subset of subjects who more closely followed the intentions of the study protocol.

**Has been changed to:**

The primary efficacy variable will also be analyzed for the PPS. This analysis set will provide additional information on the analysis of the primary efficacy variable and the impact of the important protocol deviations on efficacy.

**Change #15**

**Section 5.1 Subject disposition**

The date of first subject in, date of last subject out, number of enrolled subjects, and the number of subjects randomized, number of subjects in each treatment group, and overall, and the number of subjects in each analysis set (SS, FAS, PPS and PK-PPS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

**Has been changed to:**

The date of first subject in, date of last subject out, number of enrolled subjects, and the number of subjects randomized, number of subjects in each treatment group, and overall, and the number of subjects in each analysis set (SS, FAS, PPS and PK-PPS), will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

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 subjects data listings.

**Change #16**

**Section 5.2 Protocol deviations**

Important protocol deviations defined in the SPD, and additionally identified at the DEM before unblinding of the database will be listed including their associated categories (safety, efficacy or

study conduct). 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 for the SS. The number and percentage of subjects with no important protocol deviations will also be summarized for the SS.

**Has been changed to:**

Important protocol deviations defined in the important protocol deviation document, and additionally identified at the DEMs before unblinding of the database 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 for the SS. The number and percentage of subjects with no important protocol deviations will also be summarized for the SS.

**Change #17**

**Section 6.1 Demographic and baseline characteristics**

Age, age category ( $\geq 4$  to  $< 12$ , and  $\geq 12$  to  $< 17$  years of age), gender, race (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other/Mixed), ethnicity (Hispanic or Latino, and not Hispanic or Latino), weight (kg), height (cm), BMI ( $\text{kg}/\text{m}^2$ ), BMI category ( $< 18.5$ ,  $18.5$  to  $< 25$ ,  $25$  to  $< 30$ ,  $\geq 30$   $\text{kg}/\text{m}^2$ ), and head circumference will be summarized by treatment group and overall for the SS, and repeated by treatment group and age group, using the levels defined in section 4.8.

**Has been changed to:**

Age, age category ( $\geq 4$  to  $< 12$ , and  $\geq 12$  to  $< 17$  years of age), EudraCT age category ( $\geq 24$  months to  $< 12$  years, and  $\geq 12$  to  $< 18$  years), gender, weight (kg), weight band ( $< 30$ ,  $\geq 30$  to  $< 50$ ,  $\geq 50$  kg), height (cm), BMI ( $\text{kg}/\text{m}^2$ ), 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), and vagus nerve stimulation (VNS) use (Active VNS, No VNS, and VNS not active) will be summarized by treatment group and overall for the SS, and repeated by treatment group and age group, using the levels defined in section 4.8.

**Change #18**

**Section 6.4 Prior and concomitant medications**

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

Medications will be attributed to the study periods as defined in section 3.2.2 based on the start date of the medication.

**Section 6.4.1 Number of Lifetime AEDs**

The number of lifetime AEDs defined as AEDs taken and stopped  $> 28$  days prior to Visit 1 (ie, prior to entry into the Baseline Period), will be summarized by treatment group and overall for the SS based on the following categorization: 1 to 3 AEDs, 4-6 AEDs, and  $\geq 7$  AEDs.

**Section 6.4.2 Number of AEDs taken at study entry**

The number of AEDs taken at study entry will be summarized by treatment group and overall for the SS based on the following categorization: 1 AEDs, 2 AEDs, and 3 AEDs.

**Section 6.4.3 AEDs taken at study entry**



The number and percentage of subjects taking AEDs at the time of study entry will be summarized by WHO-DD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

#### **Section 6.4.4 Concomitant AEDs**

The number and percentage of subjects taking concomitant AEDs during the Baseline Period and during the entire Treatment Period will be summarized, separately, by WHO-DD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

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

#### **Section 6.4.5 Prior medications (excluding AEDs)**

The number and percentage of subjects taking non-AEDs at the time of study entry will be summarized by WHO-DD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

#### **Section 6.4.6 Concomitant medications (excluding AEDs)**

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

#### **Has been changed to:**

#### **Section 6.4 Prior and concomitant medications**

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

Medications will be attributed to the study periods as defined in section 3.2.2 based on the start date of the medication.

#### **Section 6.4.1 Number of Lifetime AEDs**

The number of lifetime AEDs defined as AEDs taken and stopped >28 days prior to Visit 1 (ie, prior to entry into the Baseline Period), will be summarized by treatment group and overall for the SS based on the following categorization: 1 to 3 AEDs, 4-6 AEDs, and  $\geq 7$  AEDs.

#### **Section 6.4.2 Number of AEDs taken prior to the Baseline Period**

The number of AEDs taken prior to the Baseline Period defined as AEDs with a start date prior to the date of informed consent, ie, prior to entry into the Baseline Period, excluding lifetime AEDs, will be summarized by treatment group and overall for the SS based on the following categorization: 1 AEDs, 2 AEDs, and 3 AEDs.

The number and percentage of subjects taking AEDs prior to the Baseline Period will be summarized by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

#### **Section 6.4.3 AEDs taken during the Baseline Period**

The number and percentage of subjects taking AEDs during the Baseline Period defined as AEDs with a start date on or after the date of informed consent and prior to the first dose of study medication, and AEDs with a start date prior to the date of informed consent and with a stop date on or after the start of the Baseline Period, will be summarized, separately, by WHODD

chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

#### **Section 6.4.4 Concomitant AEDs**

The number and percentage of subjects taking concomitant AEDs defined as AEDs taken concomitantly for at least one day in common with study medication will be summarized, separately, by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

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

#### **Section 6.4.5 Non-AEDs taken prior to the Baseline Period**

The number and percentage of subjects taking non-AEDs prior to the Baseline Period defined as medications with a start date prior to the date of informed consent, ie, prior to entry into the Baseline Period, will be summarized by WHODD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

#### **Section 6.4.6 Non-AEDs taken during the Baseline Period**

The number and percentage of subjects taking non-AEDs during the Baseline Period defined as medications with a start date on or after the date of informed consent and prior to the first dose of study medication, and medications with a start date prior to the date of informed consent and with a stop date on or after the start of the Baseline Period, will be summarized by WHODD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

#### **Section 6.4.7 Concomitant Non-AEDs**

The number and percentage of subjects taking concomitant non-AEDs defined as medications taken concomitantly for at least one day in common with study medication will be summarized by WHODD anatomical main group (Level 1) and therapeutic subgroup (Level 2), and by treatment group and overall for the SS.

#### **Change #19**

##### **Section 8.1.1 Derivations of primary efficacy variable**

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period.

##### **Has been changed to:**

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period. Seizure frequency per 28 days will be based on the number of days for which seizure information was provided during the specified time interval.

#### **Change #20**

##### **Section 8.2.7 Change in partial-onset seizure frequency per 28 days from Baseline to the entire Treatment Period by seizure type**

In addition, descriptive statistics for change and percent change in seizure frequency per 28 days from Baseline to each post-Baseline visit during the entire Treatment Period will be presented by treatment group and seizure type.

---

**Has been changed to:**

In addition, descriptive statistics for change and percent change in seizure frequency per 28 days from Baseline to each post-Baseline visit during the entire Treatment Period will be presented by treatment group and seizure type. Partial-onset seizure frequency per 28 days will be presented graphically at each visit by treatment group, and separately at each visit by seizure type and treatment group.

**Change #21**

**Section 8.2.8 Proportion of seizure-free days during Maintenance Period**

For all subjects who enter the Maintenance Period, the proportion of seizure free days during the Maintenance Period will be calculated.

The proportion of seizure-free days will be calculated as (days with number of seizures > 0) divided by (days with recorded data in the subject diary), where “days with recorded data in the subject diary” excludes any days where “Not Done” is recorded.

The proportion of seizure-free days during the Maintenance Period will be summarized descriptively by treatment group.

For all subjects who complete the Maintenance Period, the proportion of seizure-free days during the Maintenance Period will be calculated as described above, and summarized descriptively by treatment group.

The change in the proportion of seizure-free days from the Baseline Period to the Maintenance Period will also be presented. Only subjects with efficacy data collected during the Maintenance Period will be included/ Statistical testing for the proportion of seizure-free days will be based on an ANCOVA model with terms for treatment and pooled site and a covariate of the proportion of seizure-free days during the Baseline Period.

The proportion of seizure-free days during the Maintenance Period will also be summarized using descriptive statistics by treatment group and seizure type.

**Has been changed to:**

For all subjects who enter the Maintenance Period, the proportion of seizure-free days during the Maintenance Period will be calculated.

The proportion of seizure-free days will be calculated as (days with number of seizures = 0 during the Maintenance Period) divided by (days with recorded data in the subject diary during the Maintenance Period), where “days with recorded data in the subject diary” excludes any days where “Not Done” is recorded.

Days with missing seizure diary information will be excluded from both the numerator and denominator for the seizure-free days calculation.

For all subjects who complete the Maintenance Period, the proportion of seizure-free days during the Maintenance Period will be calculated as described above, and summarized descriptively by treatment group.

Statistical testing for the proportion of seizure-free days during the Maintenance Period will be based on an ANCOVA model with terms for treatment and pooled site and a covariate of the

proportion of seizure-free days during the Baseline Period. Only Subjects with efficacy data collected during the Maintenance Period will be included.

The proportion of seizure-free days during the Maintenance Period will also be summarized using descriptive statistics by treatment group and seizure type.

#### **Change #22**

#### **Section 8.2.9 Proportion of subjects who achieved “seizure-free” status for subjects who completed the Maintenance Period**

A subject who completed the Maintenance Period will be defined as seizure-free if they meet the following criteria:

The subject did not have any missing diary days over the Maintenance Period, that is, the seizure diary was completed for every day from Visit 6 to the day prior to the end date of the Maintenance Period.

The subject did not report any seizures during the Maintenance Period, that is, there are no diary records from the day after Visit 6 (ie, not including the date of Visit 6) up to and including the end date of the Maintenance Period with either a count >0 or a reported seizure code with an unknown or missing seizure count.

The number and percentage of subjects who achieved seizure-free status during the Maintenance Period will be presented by treatment group.

#### **Has been changed to:**

A subject who completed the Maintenance Period will be defined as seizure-free if the subject did not report any seizures during the Maintenance Period, that is, there are no diary records during the Maintenance Period with either a count >0 or a reported seizure code with an unknown or missing seizure count.

Days with missing seizure diary data will be excluded from the determination of seizure-free status as long as the percentage of days in the Maintenance Period with missing seizure diary data does not exceed 20%.

The number and percentage of subjects who achieved seizure-free status during the Maintenance Period will be presented by treatment group.

#### **Change #23**

#### **Section 8.3.6 Hospital stays**

Hospital stays will be attributed to study periods as defined in section 3.2.2 based on admission date.

The number of hospital stays per subject during the Baseline Period and during the entire Treatment Period, separately, will be summarized by treatment group. 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 Baseline Period and for the duration of the entire Treatment Period, separately, by treatment group.

Duration of hospital stays 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 Baseline Period and the duration of the entire Treatment Period, separately, by treatment group.

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 hospital stays with a discharge date. 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. The durations of hospital stays will be summed within each of the study periods defined in section 3.2.2. Subjects with no hospital stays within a study period will have a duration of 0 days for that period. Should distinct records for hospital stays overlap, then the days during the overlap will only be counted once.

All hospitalization/ER data will be listed.

**Has been changed to:**

### **Section 8.3.6 Hospital stays and emergency room visits**

Hospital stays and emergency room (ER) visits will be attributed to study periods as defined in section 3.2.2 based on admission date.

The number of hospital stays per subject during the Baseline Period and during the entire Treatment Period, separately, will be summarized by treatment group. 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 Baseline Period and for the duration of the entire Treatment Period, separately, by treatment group.

Duration of hospital stays 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 Baseline Period and the duration of the entire Treatment Period, separately, by treatment group.

An event logged on the Hospitalization/ER Visit eCRF module where ER is marked as the 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 Baseline Period and for the duration of the entire Treatment Period, will be presented, separately, by treatment group. 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 Baseline Period and the duration of the entire Treatment Period, separately, by treatment group.

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 hospital stays with a discharge date. 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. The durations of hospital stays will be summed within each of the study periods defined in section 3.2.2. Subjects with no hospital stays within a study period will have a duration of 0 days for that period. Should distinct records for hospital stays overlap, then

the days during the overlap will only be counted once. Similarly, this also applies for the ER visits.

All hospitalization/ER data will be listed.

## Change #24

### Section 10.1 Extent of exposure

All the summaries described below will also be presented for the FAS.

The overall duration of study medication exposure during each of the Titration Period, Maintenance Period, entire Treatment Period, Transition Period, and Taper Period (defined in section 3.2.2) will be calculated, as follows:

...

In addition, for the Titration Period, the number of back titration steps for each subject (categorized as: 0, 1-3, 4-6, and  $\geq 7$ ), the number of subjects with a dose change together with the number of dose changes during the interval by dose back titration occurred (categorized as:  $< 2\text{mg/kg/day}$ ,  $\geq 2\text{-} < 4\text{mg/kg/day}$ ,  $\geq 4\text{-} < 6\text{mg/kg/day}$ ,  $\geq 6\text{-} < 8\text{mg/kg/day}$ ,  $\geq 8\text{-} < 10\text{mg/kg/day}$ ,  $\geq 10\text{-} < 12\text{mg/kg/day}$ , and  $\geq 12\text{mg/kg/day}$ ,  $< 100\text{mg/day}$ ,  $\geq 100\text{-} < 200\text{mg/day}$ ,  $\geq 200\text{-} < 300\text{mg/day}$ ,  $\geq 300\text{-} < 400\text{mg/day}$ , and  $\geq 400\text{mg/day}$ ), the number of up titration steps for each subject (categorized as: 0, 1-3, 4-6, and  $\geq 7$ ), and the number of subjects with a dose change together with the number of dose changes during the interval by dose up titration occurred (categorized as:  $< 2\text{mg/kg/day}$ ,  $\geq 2\text{-} < 4\text{mg/kg/day}$ ,  $\geq 4\text{-} < 6\text{mg/kg/day}$ ,  $\geq 6\text{-} < 8\text{mg/kg/day}$ ,  $\geq 8\text{-} < 10\text{mg/kg/day}$ ,  $\geq 10\text{-} \leq 12\text{mg/kg/day}$ , and  $> 12\text{mg/kg/day}$ ,  $< 100\text{mg/day}$ ,  $\geq 100\text{-} < 200\text{mg/day}$ ,  $\geq 200\text{-} < 300\text{mg/day}$ ,  $\geq 300\text{-} < 400\text{mg/day}$ , and  $\geq 400\text{mg/day}$ ), will be summarized by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

#### Has been changed to:

All the summaries described below will also be presented for the FAS.

The overall duration of study medication exposure during each of the Titration Period, Maintenance Period, entire Treatment Period, Transition Period, and Taper Period (defined in section 3.2.2) will be calculated, as follows:

...

In addition, for the Titration Period, the number of back titration steps for each subject (categorized as: 0, 1-3, 4-6, and  $\geq 7$ ), the number of subjects with a dose change together with the number of dose changes during the interval by dose back titration occurred (categorized as:  $< 2\text{mg/kg/day}$ ,  $\geq 2\text{-} < 4\text{mg/kg/day}$ ,  $\geq 4\text{-} < 6\text{mg/kg/day}$ ,  $\geq 6\text{-} < 8\text{mg/kg/day}$ ,  $\geq 8\text{-} < 10\text{mg/kg/day}$ ,  $\geq 10\text{-} \leq 12\text{mg/kg/day}$ , and  $> 12\text{mg/kg/day}$ ,  $< 100\text{mg/day}$ ,  $\geq 100\text{-} < 200\text{mg/day}$ ,  $\geq 200\text{-} < 300\text{mg/day}$ ,  $\geq 300\text{-} < 400\text{mg/day}$ , and  $\geq 400\text{mg/day}$ ), the number of up titration steps for each subject (categorized as: 0, 1-3, 4-6, and  $\geq 7$ ), and the number of subjects with a dose change together with the number of dose changes during the interval by dose up titration occurred (categorized as:  $< 2\text{mg/kg/day}$ ,  $\geq 2\text{-} < 4\text{mg/kg/day}$ ,  $\geq 4\text{-} < 6\text{mg/kg/day}$ ,  $\geq 6\text{-} < 8\text{mg/kg/day}$ ,  $\geq 8\text{-} < 10\text{mg/kg/day}$ ,  $\geq 10\text{-} \leq 12\text{mg/kg/day}$ , and  $> 12\text{mg/kg/day}$ ,  $< 100\text{mg/day}$ ,  $\geq 100\text{-} < 200\text{mg/day}$ ,  $\geq 200\text{-} < 300\text{mg/day}$ ,  $\geq 300\text{-} \leq 400\text{mg/day}$ , and  $> 400\text{mg/day}$ ), will be summarized by treatment group, and repeated by

treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

### **Change #25**

#### **Section 10.2 Adverse events**

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

...

Other significant AEs, defined in Appendix 12 (Table 12.2), will be summarized for each treatment group by primary SOC and PT, and will be repeated by treatment group and weight group, using the levels defined in section 4.8.

#### **Has been changed to:**

AEs will be tabulated by MedDRA SOC and MedDRA PT. 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 study medication administration. Treatment-emergent adverse events (TEAE) are defined as those events which start on or after the date of first study medication administration and within 30 days following the date of last study medication administration, or whose severity worsens within this time frame. Post-treatment AEs are defined as AEs which had an onset date after 30 days after the last study medication administration.

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

...

Other significant AEs, defined in Appendix 12 (section 12.2), will be summarized for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and weight group, using the levels defined in section 4.8.

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

### **Change #26**

#### **Section 10.3 Clinical laboratory evaluations**

Observed values of hematology, chemistry, and endocrinology parameters, and change from Baseline will be summarized by treatment group for all post-Baseline visits, and Last Value.

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values which occur on or after the first study medication administration through to the end of the study.

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value will be summarized for each treatment group. Criteria for determining if a value is TEMA are detailed in Appendix 12.

**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]), and change from Baseline will be summarized by treatment group 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 treatment group and gender.

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values which occur during the defined Treatment Period (see Section 3.2.2) at scheduled or unscheduled visits on or after the first study medication administration through to the end of the Treatment Period.

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

**Change #27**

**Section 10.4.1 Vital signs, body weight, height, BMI, and head circumference**

Treatment-emergent markedly abnormal (TEMA) values are defined as those TEMA values which occur on or after the first study medication administration through to the end of the study.

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value, at each post-Baseline visit up to Visit 8, for which SBP, DBP, pulse rate, and body weight were scheduled to be assessed, and Last Value, will be presented. Percentages will be relative to the number of subjects with a value at each time point.

**Has been changed to:**

Markedly abnormal (MA) values are defined as those MA values which occur during the defined Treatment Period (see Section 3.2.2) at scheduled or unscheduled visits on or after the first study medication administration through to the end of the Treatment Period.

The number and percentage of subjects with a MA value, MA low value, and MA high value, at each post-Baseline visit up to Visit 8, for which SBP, DBP, pulse rate, and body weight were scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects with a value at each visit.

Also changed is the vital signs abnormality criteria table is now numbered 10-1.

**Change #28**

**Section 10.4.2 Electrocardiograms**

Electrocardiograms will be reviewed locally and at a central ECG laboratory. If any abnormal finding is assessed by the investigator to be clinically significant, then the ECG should be



repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

The average of the 2 interpretable readings will be used for summaries. Change from Baseline in ECG results will be summarized for all visits, and Last Value by treatment group, and will be repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

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 treatment group at Visit 1 (entry to the study), Visit 2 (Baseline), and at each post-Baseline visit up to Visit 8, and Last Value. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each time point based on the worst observed outcome across all abnormalities reported at that time point.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Value, will also be provided by treatment group 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 AEs in the Cardiac and ECG Related Terms category defined in Appendix 12 (Table 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 the 2 recordings.

**Has been changed to:**

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

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

Observed values of ECG results will be summarized for each visit and Last Visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits, and Last Visit by treatment group, and will be repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

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 treatment group at Visit 1 (entry to the study), Visit 2 (Baseline), and at each post-Baseline visit up to Visit 8, and Last Visit. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each time point based on the worst observed outcome across all abnormalities reported at that time point.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit, will also be provided by treatment group 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 (section 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.

Also changed is the electrocardiogram abnormality criteria table is now numbered 10-2.

**Change #29**

**Section 10.4.6 Tanner stage assessment**

A shift table will be produced showing the change in Tanner stage (1-5) from Baseline to Last Value, by sex and treatment group, for each of the 3-items.

**Has been changed to:**

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

**Change #30**

**Section 10.4.9.1 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 10-5.

**Table 10-5: 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
<b>BRI</b>	<b>All from {Inhibit, Shift and Emotional Control}</b>

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

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-P Professional Manual and will be reproduced programmatically.

Two validity scales will also be derived: Negativity to assess the extent to which the respondent answers selected BRIEF-P items in an unusually negative manner and Inconsistency to assess the extent to which the respondent answers similar BRIEF-P items in an inconsistent manner. The Negativity scale is the number of items in 30, 44, 46, 47, 53, 55, 56, 57, 59 and 63 with a score of 3, and so has a range of 0 to 10. A score of 2 or less is considered acceptable, 3 as elevated and 4 or more highly elevated.

For the Inconsistency scale, there are 10 item pairs of related questions. The Inconsistency scale is the sum of the absolute values of the difference in scores for the items in each item pair, and so ranges from 0 to 20. The item pairs are questions 1 and 11, 3 and 33, 5 and 45, 10 and 20, 11 and 26, 16 and 21, 18 and 52, 33 and 38, 43 and 52, and 48 and 54. A score of 7 or less is acceptable and 8 or more inconsistent.

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 at Visit 8, and Last Value, by treatment group.

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 10-5.

**Table 10-5: 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
<b>Inhibitory self-control</b>	<b>All from {Inhibit and Emotional Control}</b>
<b>Flexibility</b>	<b>All from {Shift and Emotional Control}</b>
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
<b>Emergent metacognition</b>	<b>All from {Working Memory and Plan/Organize}</b>
<b>GEC Score</b>	<b>1-63</b>

GEC=Global Executive Composite

Standardized T-scores are determined from each subject's raw GEC, inhibitory self-control, flexibility, emergent metacognition, 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 3 indexed scores and GEC for the BRIEF-P questionnaire will be summarized at Visit 8, and Last Visit, by treatment group.

All BRIEF-P assessment data will be listed.

### Change #31

#### Section 10.4.9.2 BRIEF scores

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.

Two validity scales will also be derived: Negativity to assess the extent to which the respondent answers selected BRIEF items in an unusually negative manner, and Inconsistency to assess the extent to which the respondent answers similar BRIEF items in an inconsistent manner. The Negativity scale is the number of items in 8, 13, 23, 30, 62, 71, 80, 83, and 85 with a score of 3, and so has a range of 0 to 9. A score of 4 or less is considered acceptable, 5 and 6 elevated and 7 or more highly elevated.

For the Inconsistency scale, there are 10 item pairs of related questions. The Inconsistency scale is the sum of the absolute values of the difference in scores for the items in each item pair, and so ranges from 0 to 20. The item pairs are questions 7 and 25, 11 and 22, 27 and 17, 33 and 32, 38 and 59, 41 and 65, 42 and 63, 44 and 54, 43 and 60, and 55 and 44. A score of 6 or less is acceptable, 7 and 8 questionable, and 9 or more inconsistent.

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 at Visit 8, and Last Value, by treatment group.

All BRIEF assessment data will be listed.

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**Has been changed to:**

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 at Visit 8, and Last Visit, by treatment group.

All BRIEF assessment data will be listed.

**Change #32**

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

The table Vital Signs Abnormality Criteria is numbered Table 10-1.

The table Electrocardiogram Abnormality Criteria is numbered Table 10-2.

The CBCL/1½-5 table is renumbered from Table 10-1 to Table 10-3

The CBCL/6-18 table is renumbered from Table 10-2 to Table 10-4

**13.2 Amendment 2**

The primary purpose of this amendment is to address comments raised during and after the DEM#2 and DEM#3.

**Change #1**

**Section 2.4.1 Blinded sample size re-estimation procedure**

After 50% of subjects have been randomized, completed the study (including those who discontinued), and have Baseline and post-Baseline seizure data available for analysis, a sample size re-estimation procedure will be performed in 2 consecutive stages of adjustment:

- Stage 1: Initial sample size re-estimation. An initial sample size re-estimation with equal allocation in each treatment arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011) to give a revised sample size to be adjusted in Stage 2 and Stage 3. This value will not be adjusted by more than 10% above the current estimate of 135 subjects per treatment arm (ie, the initial sample size re-estimate will not be adjusted above 149 subjects per treatment arm).
- Stage 2: Adjustment for drop-out rate. The overall study drop-out rate will be determined. The current SP0969 protocol plans for a 14% overall study drop-out rate for use in determination of sample size. If the actual overall study drop-out rate is >14%, UCB plans to adjust the sample size from Stage 1 accordingly, using an overall study drop-out rate up to a maximum of 24% (ie, the original estimated overall study drop-out rate can be increased by a maximum of 10%).

After completion of the 2 stages of sample-size re-estimation, the team will update the SP0969 protocol accordingly. UCB does not plan to reduce the sample size as a result of the blinded sample size re-estimation.

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**Has been changed to:**

After 50% of subjects have been randomized, completed the study (including those who discontinued), and have Baseline and post-Baseline seizure data available for analysis, a sample size re-estimation procedure will be performed in 2 consecutive stages of adjustment:

- Stage 1: Initial sample size re-estimation. An initial sample size re-estimation with equal allocation in each treatment arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011) to give a revised sample size to be adjusted in Stage 2 and Stage 3. This value will not be adjusted by more than 10% above the current estimate of 135 subjects per treatment arm (ie, the initial sample size re-estimate will not be adjusted above 149 subjects per treatment arm).
- Stage 2: Adjustment for drop-out rate. The overall study drop-out rate will be determined. The current SP0969 protocol plans for a 14% overall study drop-out rate for use in determination of sample size. If the actual overall study drop-out rate is >14%, UCB plans to adjust the sample size from Stage 1 accordingly, using an overall study drop-out rate up to a maximum of 24% (ie, the original estimated overall study drop-out rate can be increased by a maximum of 10%).

**Change #2**

**Section 3.2.2 Study periods**

Maintenance Period

The day after the end of the Titration Period (Visit 5) and prior to or on the end date of the Maintenance Period (Visit 8) for subjects who complete the Maintenance Period, or on or after the date of first dose of study medication and prior to or on the date of the ETV for subjects who discontinue during the Maintenance Period. If a subject does not have a Visit 8/ETV, then either the date of the last scheduled or unscheduled visit during the Maintenance Period or the date of last known dose of study medication during the Maintenance Period, whichever is later, will define the end date of the Maintenance Period.

**Has been changed to:**

Maintenance Period

The day after the end of the Titration Period (Visit 5) and prior to or on the end date of the Maintenance Period (Visit 8) for subjects who complete the Maintenance Period, or the day after the end of the Titration Period (Visit 5) and prior to or on the date of the ETV for subjects who discontinue during the Maintenance Period. If a subject does not have a Visit 8/ETV, then either the date of the last scheduled or unscheduled visit during the Maintenance Period or the date of last known dose of study medication during the Maintenance Period, whichever is later, will define the end date of the Maintenance Period.

**Change #3**

**Section 3.5.3 Per Protocol Set**

The PPS includes all subjects in the FAS who did not have important protocol deviations.

**Has been changed to:**

The PPS includes all subjects in the FAS who did not have important protocol deviations considered to have an impact on efficacy as confirmed during a DEM conducted prior to study unblinding.

**Change #4**

**Section 3.7 Center pooling strategy**

It is planned to appropriately pool centers by geographic location. The final strategy for pooling will be determined at the DEM.

**Has been changed to:**

All centers will be pooled by country for the purpose of analysis.

**Change #5**

**Section 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 study medication will be considered as concomitant medication.

Medications with a missing start date whose stop date is prior to first intake of study medication will not be considered concomitant.

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

**Has been changed to:**

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, excluding AEDs, with a missing start date whose stop date is either unknown or after the date of the first dose of study medication will be considered as concomitant medication.

AEDs with a missing start date whose stop date is unknown will be considered as lifetime AEDs. AEDs with a missing start date whose stop date is after the date of first dose of study medication will be considered concomitant.

Medications, including AEDs, with a missing start date whose stop date is prior to first intake of study medication will not be considered concomitant.

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

**Change #6**

**Section 6.4.1 Number of Lifetime AEDs**

The number of lifetime AEDs defined as AEDs taken and stopped >28 days prior to Visit 1 (ie, prior to entry into the Baseline Period), will be summarized by treatment group and overall for the SS based on the following categorization: 1 to 3 AEDs, 4-6 AEDs, and  $\geq 7$  AEDs.

**Has been changed to:**

The number of lifetime AEDs defined as AEDs taken and stopped >28 days prior to Visit 1 (ie, prior to entry into the Baseline Period), or AEDs with a missing start date and unknown stop date, will be summarized by treatment group and overall for the SS based on the following categorization: 0 AEDs, 1 to 3 AEDs, 4-6 AEDs, and  $\geq 7$  AEDs.

#### **Change #7**

Added new Section 6.4.4, so subsequent sections have been renumbered.

#### **Section 6.4.4 Number of AEDs taken on day of first dose of study medication**

The number of AEDs taken on the day of first dose of study medication will be summarized by treatment group and overall for the SS based on the following categorization: 1 AED, 2 AEDs, and 3 AEDs.

#### **Change #8**

#### **Section 7 Measurements of treatment compliance**

##### Actual weight of study medication used

Actual weight of study medication will be determined for each visit. The weight used will be computed by comparing the weight of the bottles (including adaptors and caps) of oral solution at dispensation to their weight upon return.

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

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

The actual weight used will also be determined for the Titration Period, Maintenance Period, and the entire Treatment Period (Titration+Maintenance Periods).

##### Expected weight of study medication used

Expected weight of study medication will be determined for each visit. The expected weight will be based on the actual number of days between visits, and the prescribed daily dosing of study medication oral solution.

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

Expected weight of used oral solution (g) = Daily prescribed oral solution (mL) x Number of days between visit x 1.1g/mL. Please note that 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 (Titration+Maintenance Periods).

##### Compliance

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

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 (%) = (Number of tablets dispensed – Number of tablets returned) / (Number of tablets prescribed per day (2 tablets) x Number of days between visit)) x 100

**Has been changed to:**

The total weight of used oral solution (mg) will be calculated as:

(Sum of actual weight of used oral solution [g] / 1.1g/mL) x 10mg/mL

Note that the estimated weight of 1mL of oral solution is 1.1g, and the concentration is 10mg/mL.

Where:

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

The expected weight of used oral solution (mg) will be calculated as:

Sum of daily oral solution (mg) for each day in the corresponding time period

Where:

Daily oral solution (mg) = (Morning dose [mg/kg] + Evening dose [mg/kg]) x Baseline weight (kg)

Total amount of tablets (mg) will be calculated as:

(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])

Expected amount of tablets (mg) will be calculated as:

Sum of daily tablets (mg) for each day in the corresponding time period

Where:

Daily tablets (mg) = Morning dose (mg) + Evening dose (mg)

Compliance

Compliance during a time period will be calculated using data from the respective time period only as follows:

100 x (Total weight of used oral solution [mg] + Total amount of tablets used [mg]) / (expected weight of used oral solution [mg] + expected amount of tablets [mg])

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

Compliance will be summarized separately for the Titration Period, Maintenance Period, and entire Treatment Period for the SS. It will be presented using descriptive statistics and additionally using the categorization <75%, ≥75% to ≤125%, and >125%.

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## Change #9

### Section 8.1.1 Derivations of primary efficacy variable

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period. Seizure frequency per 28 days will be based on the number of days for which seizure information was provided during the specified time interval.

Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval] divided by [number of days in the interval]) multiplied by 28.

The partial-onset seizure frequency per 28 days will be calculated for both the Baseline Period and for the Maintenance Period, and the change from Baseline calculated.

#### Has been changed to:

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period. Seizure frequency per 28 days will be based on the number of days for which seizure information was provided during the specified time interval.

Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval] divided by [number of days in the interval]) multiplied by 28.

The partial-onset seizure frequency per 28 days will be calculated for both the Baseline Period and for the Maintenance Period, and the change from Baseline calculated.

If a seizure cluster is reported, the highest recorded daily seizure frequency during the Treatment Period for the seizure type associated with the report of a seizure cluster will be used as the imputed seizure frequency for the day on which the cluster occurred.

## Change #10

### Section 8.1.2 Primary analysis of the primary efficacy variable

Seizure frequency will be analyzed using analysis of covariance with terms for treatment and center (pooled appropriately), on log-transformed seizure frequency using the transformation of  $\ln(X+1)$ , where X is the seizure frequency. Log transformed Baseline seizure frequency will be used as a covariate. The seizure frequency between treatment and placebo will be compared using the least squares means (LSMs). The percent reduction over placebo will be estimated as  $100 \times (1 - \exp[\text{LSM}_{\text{LCM}} - \text{LSM}_{\text{placebo}}])$ . A 95% CI will also be calculated for the percent reduction over placebo.

Partial-onset seizure frequency per 28 days during the Baseline Period and during the Maintenance Period, and the change from Baseline will be summarized by treatment group. This summary will be repeated by treatment group and age group, using the levels defined in section 4.8.

#### Has been changed to:

Seizure frequency will be analyzed using analysis of covariance (ANCOVA) with terms for treatment and center (pooled appropriately), on log-transformed seizure frequency using the transformation of  $\ln(X+1)$ , where X is the seizure frequency. Log transformed Baseline seizure frequency will be used as a covariate. Assumptions for the parametric model will be evaluated by diagnostic (eg, Shapiro-Wilk test for normality) and graphical methods such as residual plots,

including normal probability plots, histograms, and plots of residuals versus Baseline covariate values and treatment. An assessment will be made with regards to the influence of individual observations (eg, extreme outliers) on the analysis. To the extent feasible, such potential influential observations will be identified prior to unblinding, and an assessment will be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If deemed that a non-parametric method is warranted, an ANCOVA model on rank of seizure frequency per 28 days with terms for treatment and center (pooled appropriately) will be employed as the primary analysis. Ranked seizure frequency per 28 days during the Baseline Period will be used as a covariate.

The seizure frequency between treatment and placebo will be compared using the least squares means (LSMs). The percent reduction over placebo will be estimated as  $100 \times (1 - \exp[\text{LSM LCM} - \text{LSM placebo}])$ . A 95% CI will also be calculated for the percent reduction over placebo.

Partial-onset seizure frequency per 28 days during the Baseline Period and during the Maintenance Period, and the change from Baseline will be summarized by treatment group. This summary will be repeated by treatment group and age group, using the levels defined in section 4.8.

#### **Change #11**

##### **Section 8.3.3 PedsQL assessment**

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

Calculated values and change from Baseline for the total scale score and each of the 4 scale scores will be summarized for each visit and Last Visit by treatment group. Subgroup summaries by age will be performed using the age groupings for which different questionnaires were entered:  $\geq 2$  to  $\leq 4$  years,  $\geq 5$  to  $\leq 7$  years,  $\geq 8$  to  $\leq 12$  years, and  $\geq 13$  to  $\leq 18$  years.

##### **Has been changed to:**

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.

Calculated values and change from Baseline for the total scale score, psychosocial health score and each of the 4 scale scores will be summarized for each visit and Last Visit by treatment group. Subgroup summaries by age will be performed using the age groupings for which different questionnaires were entered:  $\geq 2$  to  $\leq 4$  years,  $\geq 5$  to  $\leq 7$  years,  $\geq 8$  to  $\leq 12$  years, and  $\geq 13$  to  $\leq 18$  years.

#### **Change #12**

##### **Section 9.1 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: arithmetic mean, SD, median, range, geometric mean, and geometric CV. The evaluations will be done based on separation by LCM maintenance dose level, and repeated by LCM maintenance dose level and age group.

##### **Has been changed to:**

The results of LCM and other AEDs plasma concentrations will be described by the method of descriptive statistics: arithmetic mean, SD, median, range, geometric mean, and geometric CV. The evaluations will be done based on separation by LCM maintenance dose level, and repeated by LCM maintenance dose level and age group.

Summarization of PK data relative to time after dose will be performed for the overall group and separated by AED therapy and possibly age groups.

### **Change #13**

#### **Section 9.2 Population pharmacokinetics**

Summarization of PK data relative to time after dose will be performed for the overall group and separated by AED therapy and possibly age groups.

A population PK modeling of the LCM concentration time data will be performed within the NONMEM software. The effects of age, body weight, AED therapy, and other covariates will be evaluated. Simulations will be undertaken for estimating dose adaptations leading to the same exposure as in adults.

The methods will be described in the Data Analysis Plan (DAP) and the results will be reported in a separate modeling report.

#### **Has been changed to:**

A population PK modeling of the LCM concentration time data will be performed within the NONMEM software. The effects of age, body weight, AED therapy, and other covariates will be evaluated. Simulations will be undertaken for estimating dose adaptations leading to the same exposure as in adults.

The methods will be described in the Data Analysis Plan (DAP) and the results will be reported in a separate modeling report.

### **Change #14**

#### **Section 10.1 Extent of exposure**

All the summaries described below will also be presented for the FAS.

The overall duration of study medication exposure during each of the Titration Period, Maintenance Period, entire Treatment Period, Transition Period, and Taper Period (defined in section 3.2.2) will be calculated, as follows:

Titration Period: date of last dose of study medication during the Titration Period minus the date of first dose of study medication plus 1.

Maintenance Period: date of last dose of study medication during the Maintenance Period minus the date of first dose of study medication during the Maintenance Period plus 1.

Entire Treatment Period: date of last dose of study medication during the entire Treatment Period minus the date of first dose of study medication plus 1.

Transition Period: date of last dose of study medication during the Transition Period minus the date of first dose of study medication during the Transition Period plus 1.

Taper Period: date of last dose of study medication during the Taper Period minus the date of first dose of study medication during the Taper Period plus 1.

Entire study: date of final dose of study medication minus the date of first dose of study medication plus 1.

The overall duration of study medication exposure will be summarized for each of the study periods defined above, and also for the entire study by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

In addition, the overall duration of study medication exposure will be summarized using the following categories for each of the study periods defined above, and also for the entire study by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8:

Titration Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks, and  $>4-\leq 6$  weeks.

Maintenance Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks, and  $>8-\leq 10$  weeks.

Entire Treatment Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks,  $>8-\leq 10$  weeks,  $>10-\leq 12$  weeks,  $>12-\leq 14$  weeks, and  $>14-\leq 16$  weeks.

Transition Period:  $\leq 2$  weeks, and  $>2-\leq 4$  weeks.

Taper Period:  $\leq 2$  weeks, and  $>2-\leq 4$  weeks.

Entire study:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks,  $>8-\leq 10$  weeks,  $>10-\leq 12$  weeks,  $>12-\leq 14$  weeks,  $>14-\leq 16$  weeks,  $>16-\leq 18$  weeks,  $>18-\leq 20$  weeks,  $>20-\leq 22$  weeks, and  $>22-\leq 24$  weeks.

**Has been changed to:**

The overall duration of study medication exposure during each of the Titration Period, Maintenance Period and entire Treatment Period (defined in section 3.2.2) will be calculated, as follows:

Titration Period: date of last dose of study medication during the Titration Period minus the date of first dose of study medication plus 1.

Maintenance Period: date of last dose of study medication during the Maintenance Period minus the date of first dose of study medication during the Maintenance Period plus 1.

Entire Treatment Period: date of last dose of study medication during the entire Treatment Period minus the date of first dose of study medication plus 1.

The overall duration of study medication exposure will be summarized for each of the study periods defined above by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8.

In addition, the overall duration of study medication exposure will be summarized using the following categories for each of the study periods defined above by treatment group, and repeated by treatment group and age group, and by treatment group and weight group using the levels defined in section 4.8:

Titration Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks, and  $>4-\leq 6$  weeks.

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Maintenance Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks, and  $>8-\leq 10$  weeks.

Entire Treatment Period:  $\leq 2$  weeks,  $>2-\leq 4$  weeks,  $>4-\leq 6$  weeks,  $>6-\leq 8$  weeks,  $>8-\leq 10$  weeks,  $>10-\leq 12$  weeks,  $>12-\leq 14$  weeks, and  $>14-\leq 16$  weeks.

### **Change #15**

#### **Section 10.4.4.1 Complete neurological examination**

...

Summaries of shift from Baseline to Last Visit will be provided by treatment group 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.

#### **Has been changed to:**

...

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

### **Change #16**

#### **Section 10.4.4.1 Brief neurological examination**

...

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

#### **Has been changed to:**

...

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

### **Change #17**

#### **Section 10.4.7 Achenbach Child Behavior Checklist**

The syndrome scale “Emotionally reactive” originally had 28 as a question instead of 82.

**Table 13–3: 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, 77, 80, 89, 91, 100

**Has been changed to:**

**Table 13–4: 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

**Change #18**

**Section 12.2 Other significant adverse events**

Removed the footnote from the table as this was not applied to the programming of other significant adverse events.

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## 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 Statistical Analysis Plan (SAP) or amended SAP is released for execution.

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## sp0969-Statistical Analysis Plan-Amendment 2

### ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[REDACTED]	Clinical Approval	09-Feb-2017 22:24 GMT+01
[REDACTED]	Clinical Approval	09-Feb-2017 23:20 GMT+01
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