STATISTICAL ANALYSIS PLAN

Study: SP0982

Product: Lacosamide

A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017
Amendment #2	14 Mar 2017
Amendment #3	4 Jan 2019
Amendment #4	28 Mar 2019

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BMI	body mass index
BP	Blood pressure
BRI	Behavioral Regulation index
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool version
CB	combined baseline
CBCL	Child Behavior Checklist
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
ET	Early Termination
EQ-5D-3L	3-Level EuroQol-5 Dimension Quality of Life Assessment
FAS	Full Analysis Set
GEC	Global Executive Composite
GGT	Gamma glutamyl transferase
HR	hazard ratio
HRQoL	health-related quality of life
IDMC	independent data monitoring committee
IGE	idiopathic generalized epilepsy
II	Generalized seizures
IIA	Absence seizures
IIB	Myoclonic seizures
IIC	Clonic seizures
IID	Tonic seizures
IIE	(primary generalized) tonic-clonic seizures
IIF	Atonic seizures

III	Unclassified seizures
ILAE	International League Against Epilepsy
IRT	Interactive response technology
KM	Kaplan-Meier
LCM	Lacosamide
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Metacognition Index
NCI CTC	National Cancer Institute Common Terminology Criteria for Adverse Events
PCH	percent change
PedsQL	Pediatric Quality of Life Inventory
PGTC	primary generalized tonic-clonic
PGTCS	Primary generalized tonic-clonic seizure
PH	proportional hazard
PHREG	proportional hazards regression
PPS	Per-Protocol Set
PT	preferred term
QOLIE-31-P	Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31
QTcB	Bazett corrected QT
QTcF	Fridericia corrected QT
RS	Randomized Set
SAP	Statistical Analysis Plan
SAS®	Statistical analysis software
ScS	Screened Set
SF	seizure frequency
SOC	system organ class
SS	Safety Set
TEAE	treatment emergent adverse event
TEMA	treatment emergent markedly abnormal
ULN	upper limit of normal
VAS	visual analog scale
VNS	vagus nerve stimulation
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of the statistical analysis plan (SAP) is to describe the analyses of study SP0982.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary study objective is to demonstrate the efficacy of oral lacosamide (LCM) vs placebo as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures (PGTCS) in subjects with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant antiepileptic drugs (AEDs) independent of the number of prior failed AEDs.

2.1.2 Secondary objective

The secondary study objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTCS.

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable is the time to the second PGTCS during the 24-week Treatment Period.

2.2.1.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Seizure freedom for PGTCS during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variable is:

- Time to first seizure during the 24-week Treatment Period

2.2.1.3 Other efficacy variables

Other efficacy variables are:

- The percent change in PGTCS frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Combined Baseline Period (combined 12-week Historical and 4-week Prospective Baseline Periods)
- The percent change in PGTCS frequency per 28 days during the first 12 weeks of the Treatment Period relative to the Combined Baseline Period
- The percent change in PGTCS frequency per 28 days during the Treatment Period relative to the Combined Baseline Period
- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period

- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline Period
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Prospective Baseline Period
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline Period
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Prospective Baseline Period
- Seizure-free status (yes, no) for PGTCS for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTCS for the 24-week Treatment Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the Titration Period compared to Combined Baseline Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the first 12 weeks of the Treatment Period compared to Combined Baseline Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the Treatment Period compared to Combined Baseline Period
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- Change from Baseline to end of treatment or early termination (ET) in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject due to epilepsy

- Number of days with help from a caregiver due to epilepsy

2.2.2 Safety variables

The safety variable is:

- Adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the investigator

2.2.2.1 Other safety variables

Other safety variables are:

- Subject withdrawal due to AEs
- Incidence of new seizure types during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Changes in hematology, chemistry, endocrinology, and urinalysis parameters
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings
- Behavioral assessment (Achenbach Child Behavior Checklist [CBCL]/1½-5 or CBCL/6-18)
- Cognitive function assessment (Behavior Rating Inventory of Executive Function®-Preschool Version [BRIEF-P] or Behavior Rating Inventory of Executive Function® [BRIEF]) for pediatric subjects only

2.2.3 Pharmacokinetic variables

The plasma concentrations of LCM will be assessed.

2.3 Study design and conduct

2.3.1 Study description

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM vs placebo as adjunctive therapy for uncontrolled PGTCS in subjects ≥4 years of age with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs.

Up to 250 subjects across 150 to 180 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study to see 125 events. An event is the occurrence of each subject's second PGTCS. The maximum duration of study medication administration is 28 weeks. The study will last a maximum of 36 weeks per subject.

Eligibility to enter SP0982 will be based on a 12-week Historical Baseline prior to screening at Visit 1. In rare cases where there is a gap between consenting and Visit 1 procedures, the 12-week Historical Baseline will be calculated from the date of Informed Consent/Assent.

Prior to randomization, the following 3 criteria concerning PGTCS frequency must be met:

- The subject must have experience at least 3 PGTCS during the 16-week Combined Baseline Period,
- The subject must have experienced at least 2 PGTCS during the 12-week Historical Baseline Period,
- Of the above seizures, at least 1 PGTCS should have occurred during the first 8 weeks and at least 1 PGTC seizure should have occurred during the second 8 weeks of the 16-week Combined Baseline Period.

Examples of different scenarios and the subjects' eligibility in terms of Baseline Period PGTCS are presented in Table 1 . Seizures reported on the Historical Seizure Count CRF with incomplete dates will be assumed to have occurred with the 12-week Historical Baseline Period when checking eligibility for the study and inclusion in baseline PGTCS frequency per 28 days.

Table 1: Number of PGTC Seizures for Study Entry

Number of PGTCS for Study Entry			Subject Eligible for Study?
Historical Baseline Weeks -16 to -9	**Historical Baseline** Weeks -8 to -5	**Prospective Baseline** Weeks -4 to 0 (Visit 1 to Visit 2)	
2	1	0	Yes
3	0	0	No
1	1	1	Yes
0	2	1	No
1	2	0	Yes
2	0	1	Yes
1	0	2	No
1	1	0	No

The study consists of a 4-week Prospective Baseline Period and a 6-week (minimum) to 24-week (maximum) Treatment Period, which includes a 6-week Titration Period and an 18-week (maximum) Maintenance Period. Eligible subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 10 (Week 24) or the ET Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period.

At the end of the 4-week Prospective Baseline (Visit 2), eligible subjects will be randomized to receive LCM or placebo in a 1:1 fashion (active:placebo) and stratified by Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days for the 16 week Combined Baseline Period prior to randomization) and by age at informed consent (≥4 to <12 years of age vs ≥12 to <18 years of

age, and ≥18 years of age). The Treatment Period starts at the time of the Randomization Visit (Visit 2).

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTCS
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTCS
- Occurrence of the 125th event (an event is each subject's 2nd second PGTCS).

Subjects will be required to exit the study and complete the ET Visit if either of the following events occur:

- Subject completes the first 6 weeks of the Treatment Period (after randomization) and experiences ≥2 PGTCS during that time
- Subject experiences a second PGTCS after the first 6 weeks of the Treatment Period

If the 125th event occurs while the subject is still participating in the study, the subject can:

- Complete the Visit 10 (Week 24) or ET Visit (if the next scheduled visit is not Visit 10) and choose to continue in EP0012 by completing a blinded transition followed by a Final Clinic Visit.
- Discontinue from the study by completing the Visit 10 (Week 24) or ET Visit (if the next scheduled visit is not Visit 10) and an up to 4-week blinded taper followed by an End of Taper visit.

The study design is discussed in more detail in Section 5 of the protocol.

2.3.2 Rationale for study design

Clinical experience has shown that up to 30% of patients with PGTCS who are treated with currently available AEDs have insufficient PGTCS control or unacceptable drug tolerability. Thus, there is a significant unmet medical need for new treatment options in this patient population.

The primary efficacy variable, the time to the second PGTCS, has several advantages from a clinical and methodological perspective. In traditional adjunctive study designs, the primary endpoint is percent reduction in PGTCS frequency over the entire Treatment Period; which requires a higher frequency of PGTCS at entry. Using the time to second PGTCS, the frequency of Baseline PGTCS and the duration of the Prospective Baseline can be reduced as the endpoint is time to reach an event (second PGTCS), rather than a percentage decrease in the number of events (PGTCS). This expands the patient population under study and allows for enrollment of subjects more representative of the broader PGTCS population. Furthermore, subjects are treated for up to 24 weeks in a traditional adjunctive design, depending upon the titration schedule of the active treatment. Subjects must remain on treatment as they continue to experience PGTCS. In the time to nth seizure design, subjects are required to remain in the study for a minimum of 6 weeks. If a subject experiences ≥2 PGTCS while on treatment, then after 6 weeks the subject exits the study, rather than continuing to have PGTCS, while remaining eligible to receive LCM in the open-label extension study (EP0012).

The rationale for time to second PGTCS was established by using data from an adjunctive study in subjects with PGTCS, using an 8-week Baseline, 7-week Titration, and 12-week Maintenance Period comparing lamotrigine and placebo (French et al, 2007). This post-hoc analysis using a Cox proportional hazards model revealed that time to third PGTCS was statistically significant with a hazard ratio of 0.533 (lamotrigine 48.2%, placebo 25.4%). Lamotrigine requires a long Titration Period, where a minimally effective dose is not reached until the fifth week of the Titration Period (100mg/day). Lacosamide, by comparison, reaches a minimally effective dose in the second week (200mg/day) for a majority of trial subjects. Since a majority of the events in the lamotrigine study occurred before Day 21, it is likely that fewer events would occur using LCM as it reaches an effective dose earlier; therefore, time to second PGTCS was chosen as a reasonable endpoint from a clinical and statistical perspective.

2.4 Determination of sample size

Observing 125 events (subjects who had a second PGTCS during the 24-week Treatment Period) will provide 90% power to observe a hazard ratio of 0.56 at the 2-sided 5% level, assuming a dropout rate of 15%. The observed hazard ratio was based on a 25.4% survival rate for placebo and 48.2% for lamotrigine from a previous study comparing lamotrigine and placebo (French et al, 2007). The observed hazard ratio in the lamotrigine study was 0.533; however, in order to account for the possibility of an increased placebo response, as has been documented in recent clinical studies of AEDs, the hazard ratio was increased by 5% to 0.56 for estimating a sample size for this study. The rationale for the increase in the hazard ratio included the following considerations: different active compounds (LCM and lamotrigine) and a choice of time to second PGTCS as the primary efficacy endpoint (in the lamotrigine study, percent change in PGTCS frequency was the primary endpoint).

This is an event-driven study. Enrollment in the study will continue up to 125 events occurring or a maximum of 250 subjects randomized, whichever comes first.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS® Version 9.4 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be used to provide an overview of the primary, secondary, and other variable 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 the 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, mean, standard deviation, median, minimum, and maximum.

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

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

By-visit summaries will not include data from unscheduled clinic visits unless otherwise stated. Data provided at these visits will be included in subject data listings. A complete set of data listings containing all documented data and all calculated data (eg, change from Baseline) will be generated.

3.2 General study level definitions

3.2.1 Analysis time points

The following study periods will be defined for analyses:

- Historical Baseline Period: This period starts 84 days prior to Visit 1 and ends the day before Visit 1. This is expected to be 12 weeks in duration.
- Prospective Baseline Period: This period starts the date of Visit 1 and ends the day before Visit 2. This is expected to be 4 weeks in duration.
- Combined Baseline Period: combined Historical and Prospective Baseline Periods. This Period starts 84 days prior to Visit 1 and ends the day before Visit 2. This is expected to be 16 weeks in duration.
- Treatment Period: 24-week period following the 4-week Prospective Baseline. The Treatment Period is composed of the Titration Period and the Maintenance Period.
  - Titration Period: 6-week period following the 4-week Prospective Baseline. The Titration Period starts on the date of the Randomization Visit (Visit 2) and ends on the day before Visit 5 (or the date of the Early Termination (ET) visit in the situation where a subject discontinues prior to the last visit in the Titration Period).
  - Maintenance Period: 18-week period following the 6-week Titration Period. The Maintenance Period starts on the day of Visit 5 and continues until 1 of the following occurs (whichever occurs first):
    - Completion of ≥6 weeks of the Treatment Period, occurrence of ≥2 PGTC seizures and completion of the ET Visit
    - Completion of 18 weeks (Visit 10) of the Maintenance Period without occurrence of 2 PGTC seizures.
  - First 12 weeks: this is defined as the Titration Period + the first 6 weeks of the Maintenance Period.
- Transition Period: up to 4-week period after the completion of Visit 10 (Week 24) or the ET Visit for subjects who choose to enter EP0012. The Transition Period starts the day after Visit 10 (Week 24) or the ET Visit and continues until 1 of the following occurs (whichever occurs first):
    - On the day before the first date that there is a dose decrease (subject enters Taper period)
    - On the date of the Final Clinic Visit (also date of EP0012 Visit 1).
- Taper Period: up to 4-week period following either the Treatment Period for subjects who discontinue from the study at any time and are not eligible or choose not to enter EP0012 or

following the Transition Period for subjects that discontinue from the study during the Transition Period. The Taper Period starts the first date that there is a dose decrease or the day after the ET Visit for subjects that choose not to enter EP0012 and continues until the date of last dose of study medication.

- Safety Follow-up Period: period following the Taper Period for subjects who complete the Taper Period. The Safety Follow-up Period starts the day after the last dose of study medication and continues until the Final Clinic Visit date or the Safety Follow-up telephone contact date, whichever is later.

3.2.2 Seizure cluster

If a seizure cluster is reported, it will be assigned to the International League Against Epilepsy (ILAE) seizure type reported and the frequency will be set to 2 times the number of clusters reported.

3.2.3 Event

In the primary efficacy analysis, an event for analysis purposes is:

- The 2nd PGTCS

While keeping in mind the definition of seizure clusters in Section 3.2.2.

For the primary and secondary efficacy analyses, these endpoints will be assessed using the at most the first 166 days, which is the 24-week Treatment Period minus a protocol-allowed 2 day window. For all other efficacy parameters, all data reported during the Treatment Period will be used in the analysis.

The primary efficacy endpoint, time to event, is defined as the "stop date" - the date of first dose of study drug + 1 day where the "stop date" is the first of the following to occur:

- date of the event,
- date of the premature discontinuation,
- date of last dose of study medication in the Treatment Period,
- date of the completion of the Treatment Period,
- date of the 125th event,
- Day 166

The same algorithm applies for the other secondary endpoint, where time to event, is replaced by time to 1st PGTCS.

3.2.4 Censoring

For the primary and secondary efficacy analyses, a Treatment Period of 166 days will be utilized. The censoring for the primary efficacy analysis will be as follows:

- Subjects who complete the Treatment Period without having an event during the Treatment Period will be censored as of Day 167.

- If the subject's Treatment Period participation is less than or equal to 166 days (premature discontinuation), their PGTCS information will be censored on the date after the last dose of study drug.
- If the subject's Treatment Period participation is greater than 166 days, their PGTCS information will be censored as of Day 167.
- For the subjects who are ongoing in the study when the 125th event occurs, their PGTCS information for the primary efficacy endpoint analysis will be censored as of the day after the 125th event, even if the subjects experience an event after the date of the 125th event but before 166 days of treatment is completed.
- Only 125 events will be included in the primary efficacy endpoint analyses. In case of ties on the same date in reporting the 125th event, the first event reported to IRT will be deemed the 125th event. Data after the 125th event will be censored.

Censoring for time to 1st PGTCS will be calculated in a similar manner, except using the date of the 1st PGTCS instead of the date of the event. For subjects who are ongoing in the study when the 125th event occurs, the time to 1st PGTCS information will be censored in the same manner as the time to event information (ie., censor all PGTCS information beyond the date of the 125th event).

3.2.5 AEDs and benzodiazepines

AEDs and benzodiazepines (medications used for rescue) will be collected on the concomitant and prior medication case report form (CRF) for AEDs. At study entry, a subject should be taking a stable dose of 1 to 2 non-benzodiazepines marketed AEDs or 2 to 3 AEDs (with only 1 of the AEDs is identified as a benzodiazepine). This dosing regimen must be stable for at least 28 days prior to Visit 1. The subject must maintain this AED dosing regimen throughout the Prospective Baseline and the Treatment Period with or without additional concurrent stable VNS. Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and must remain unchanged during the Treatment Period.

AEDs at study entry are defined as AEDs where the start date is on or before 28 days prior to Visit 1 and the medication was still ongoing on the date of Visit 1. Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to Visit 1.

Benzodiazepines taken for rescue will be flagged with "RESCUE" in the indication field on the CRF, although rescue AEDs will also be identified programmatically as any AED taken intermittently for 1 or 2 days, at any frequency, with an epilepsy or seizure related indication. Rescue medication is defined as the intermittent use of benzodiazepines (limited to 2 doses per 28 days) for epilepsy indications if established at least 28 days prior to Visit 1. Lifetime benzodiazepines are defined as benzodiazepines taken in the subject's history and stopped at least 28 days prior to Visit 1.

3.2.5.1 Prohibited concomitant treatments (medications and therapies)

The following medications/therapies are prohibited during the Treatment Period:

- Clozapine

- Any MAO inhibitors
- Barbiturates (except as antiepileptic medications)
- Unstable dosing of non-benzodiazepine anxiolytics or once-daily hypnotics
- Herbal medicines for epilepsy

The study physician will review the concomitant medications and flag prohibited medications.

3.2.6 Relative day

Relative day will be presented in most subject data listings. Relative day will be calculated as follows:

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

Subjects with missing or incomplete dates will also have a missing relative day.

3.2.7 Last Visit

Last Visit is defined as the last post-Baseline non-missing visit (including unscheduled visits) during the Treatment Period.

3.2.8 Month

A month is defined as 28 days.

3.3 Definition of Baseline values

Data collected at Visit 2 prior to the first dose of study medication (physical examination, neurological examination, ECG, vital signs, laboratory tests) will be used as Baseline values. Data collected on the date of first dose of study medication will be assumed to be prior to the first dose. For quantitative ECG assessments, if repeat measurements pre-dose, then the average value is used as the Baseline value. For data not collected at Visit 2 prior to the first dose of study medication, the last data collected prior to the first dose of study medication will be used as Baseline values.

For PGTCS efficacy analyses, the data used for Baseline calculations come from the Combined Baseline Period. For absence and myoclonic seizure analyses, the data used for Baseline calculations come from the Prospective Baseline Period only.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on either 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 within the project Data Cleaning Plan. 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 in a blinded manner as part of the ongoing data cleaning process prior to database lock to confirm exclusion from the Per Protocol Set (PPS).

3.5 Analysis sets

The Safety Set (SS) will serve as the primary population for assessing safety endpoints. The Full Analysis Set (FAS) will serve as the primary population for assessing efficacy endpoints.

3.5.1 Screened Set

The Screened Set (ScS) consists of all subjects who have entered screening at Visit 1, have a signed Informed Consent/Assent Form, and have at least basic demographic data available.

3.5.2 Randomized Set

The Randomized Set (RS) is a subset of the ScS and consists of all subjects who were randomized at the Randomization Visit (Visit 2).

3.5.3 Safety Set

The SS is a subset of the RS and consists of all subjects who have been treated with at least 1 dose of study drug, either LCM or placebo. This population will serve as the primary population for assessing safety endpoints.

3.5.4 Full Analysis Set

The FAS is a subset of the SS consisting of all subjects with at least 1 seizure diary assessment during the Treatment Period. This population will serve as the primary population for assessing efficacy endpoints.

3.5.5 Per Protocol Set

The PPS is a subset of the FAS excluding subjects who completed fewer than 6 weeks of treatment or subjects with important protocol deviations affecting the interpretation of the primary efficacy analysis. Important protocol deviations will be determined prior to database lock and unblinding.

3.6 Treatment assignment and treatment groups

Safety data summaries will be presented by randomized treatment and sometimes by overall, while efficacy data summaries will be presented by randomized treatment. Treatments will be reported as LCM and placebo, and in some cases, by all subjects.

If a subject receives a treatment other than the randomized treatment, an evaluation of the mis-treatment will be made to determine if the subject should be summarized under a different treatment arm for safety assessments. Data obtained from subjects who receive an incorrect kit

will be reviewed and the study team will determine how to handle such cases in the statistical analyses prior to database lock and unblinding.

3.7 Center pooling strategy

Refer to Section 4.4.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD, SEP/2013). All coding will be completed prior to database lock and unblinding.

3.9 Changes to protocol-defined analyses

For the key secondary efficacy variable, the Protocol Section 4.1.2 says that seizure freedom for PGTCS during the 24-week Treatment Period, will be estimated using Kaplan-Meier analysis. Also, Protocol Section 13.3.2.1 states that the key secondary efficacy variable will be analyzed in the same manner as the primary endpoint using the FAS and that the percentage of seizure-free subjects at 24 weeks will be estimated from the KM estimates of time to first seizure. The analysis of the key secondary endpoint has been clarified to assess the seizure-free rate at 24 weeks using an extended Mantel-Haenszel technique which combines Kaplan-Meier estimates within each stratum. The extended Mantel-Haenszel technique is a randomization-based nonparametric method that provides a more robust method to assess seizure freedom. Thus, the key secondary efficacy variable will not be analyzed in the same manner as the primary efficacy endpoint; the other secondary efficacy variable, time to first PGTCS, will be analyzed in the same manner as the primary efficacy endpoint.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Analyses of the primary efficacy variable and several other efficacy variables will be adjusted for the stratification variables Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days for the 16 week Combined Baseline Period prior to randomization) and age at informed consent (≥4 to <12 years of age vs ≥12 to <18 years of age, and ≥18 years of age). Stratification factors recorded at randomization in the interactive response technology (IRT) will be used.

4.2 Handling of dropouts or missing data

4.2.1 Missing seizure diary days

For evaluations based on seizure diary data, imputation for missing data will not be performed.

For the purpose of the derivation of the primary efficacy endpoint, secondary efficacy endpoints and for PGTC seizure-free status, if there are PGTCS counts reported as “not done” on a specific day, then the PGTCS count will be assumed to be zero on that date.

The calculation of average 28-day PGTCS frequency accounts for missing data by only evaluating days for which data are available.

4.2.2 Incomplete dates for first epilepsy diagnosis

To calculate the time since first epilepsy diagnosis, a complete date will be imputed for partially missing first diagnosis date. First diagnosis dates will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listing).

- Missing the day, but month and year present:

Assign the 1st day of the month or the subject's birthday (imputing 1st for the day if only month and year are collected), whichever is later.

- Missing the day and month, but year present:

Assign January 1st of the year or the subject's birthday, whichever is later.

- Missing the day, month and year:

No imputation will be done.

4.2.3 Incomplete dates for adverse events and concomitant medications

The following rules are applied to impute partial start and stop dates for medications. The date as recorded on the CRF should be presented in subject data listings (no imputed dates should be included in subject data listings).

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the first day of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use January 1st of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose.
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.

Imputation of Partial Stop Dates

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then the end day and month will be set to the maximum of the date of study termination or the date equivalent to 30 days after the last intake of LCM. However, if the study termination year and year for the date which is 30 days after last intake of LCM are greater than the concomitant medication year, then the day and month are to be set to December 31st.
- If the stop date is completely unknown, do not impute the stop date.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant.

The following rules are applied to impute partial onset and resolution dates for AEs. AEs with partial onset date are classified as either non-treatment- or treatment-emergent based on the imputed onset date.

Imputation of Partial Onset Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of onset, then use the first day of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of onset, then use the date of first dose.
- If only the year is specified, and the year of first dose is not the same as the year of onset, then use January 1st of the year of onset.
- If only the year is specified, and the year of first dose is the same as the year of onset, then use the date of first dose.
- If the AE onset date is completely unknown, then use the date of first dose.

Imputation of Partial Resolution Dates

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then the end day and month will be set to the maximum of the date of study termination or the date equivalent to 30 days after the last intake of LCM. However, if the study termination year and year for the date which is 30 days after last intake of LCM are greater than the event year, then the day and month are to be set to December 31st.
- If the AE resolved and the resolution date is completely unknown, then do not impute the resolution date.

4.2.4 Incomplete date for the last administration of study medication

No imputation should be performed for missing study medication start dates. This field on the CRF should not be partial or missing.

For partial or missing date of last dose of study medication, the following imputation rules will be applied for the purpose of calculating overall exposure:

- If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the Study Termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the Study Termination CRF.
- If a subject died and has a partial or missing last administration date, the date is set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.
- If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact according to the Study Termination CRF. A review of the data for subjects with completely missing last

dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.

Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the CRF should be presented in subject data listings (no imputed dates should be included in subject data listings).

4.2.5 Missing adverse event intensity

If the intensity of an AE is missing then it will be counted as severe for analysis purposes.

4.2.6 Missing adverse event relationship to study medication

If the AE relationship to study medication is missing then it will be counted as related for analysis purposes.

4.3 Interim analyses and data monitoring

To enhance safety monitoring, 3 interim analyses are planned when 25%, 50%, and 75% of subjects experience an event (31, 62, and 93 events, respectively) or 24 weeks after 50, 100, and 150 subjects have been randomized, respectively, whichever comes first. An event is defined as the occurrence of the second PGTCS during the Treatment Period.

These interim reviews for safety will be performed using an Independent Data Monitoring Committee (IDMC), with a single futility assessment planned at the second interim analysis. The IDMC will oversee the safety of the study by reviewing safety data periodically. Details are provided in an IDMC charter. Both safety and futility will be assessed in a manner that ensures that blinding is not compromised for individuals involved with operational aspects of the study, nor individuals involved with the planning and conduct of the final statistical analyses. Analysis of the primary efficacy endpoint (time to second PGTCS) will only be examined at the planned futility assessment; an unblinded, descriptive review of safety and seizure data will be provided for all IDMC meetings.

No consideration will be made for stopping due to early demonstration of efficacy; however, the significance level will be set using a Haybittle-Peto boundary at alpha=0.0001 so as to require only a nominal alpha adjustment for the final analysis. Full details of the interim analysis are described in the Interim Analysis Statistical Analysis Plan.

4.4 Multicenter studies

Due to the small number of subjects per site, all sites will be pooled together for analysis. There will be no planned analyses for multi-center effects.

4.5 Multiple comparisons/multiplicity

A gatekeeping strategy (Marcus et al, 1996) will be used to test the key secondary efficacy variable provided that the primary efficacy endpoint is statistically significant (See Section 8.2.1 for additional details). No additional adjustments for multiplicity are required as all additional inferences will be hypothesis-generating only.

4.6 Use of an efficacy subset of subjects

The PPS will be used to evaluate subjects who completed at least 6 weeks of treatment and have no important protocol deviations related to the primary efficacy variable. 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.

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

Descriptive statistics by all subgroups for the primary efficacy variable will be presented for the FAS. Disposition will be presented by age subgroup for the SS and FAS. Exposure will be presented by age and region subgroups for the SS. Overall TEAE incidence will be presented by age subgroup for the SS. Selected disposition and safety analyses will be presented by Development for the purpose of addressing requirements set in Article 46 of the European Pediatric Regulation (see Section 12.5 for further details).

The subgroups to be examined include:

- Age at enrollment (≥ 4 to <12 years of age, ≥12 to <18 years of age, 18 to <65, ≥65)
- Development (Pediatric [≥4 to < 18 years old], Adult [≥18 years old])
- Racial group (white, non-white)
- Gender (male, female)
- Region
  - North America: United States, Puerto Rico
  - Latin America: Brazil, Mexico
  - Western/Central Europe: Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain
  - Eastern Europe: Bulgaria, Romania, Russia, Turkey
  - Asia/Pacific/Other: Australia, China, Israel, Japan, South Korea, Taiwan
- Baseline PGTCS frequency (≤2 per 28 days and >2 per 28 days in the Combined Baseline Period)
- Concomitant AEDs at study entry, ie the total number of AEDs and benzodiazepines the subject is taking when enrolled into the study (1, 2, 3).

Separate age sub-groupings are used for the purpose of summarizing the following scales:

- PedsQL (4 years, ≥5 to ≤7 years, ≥8 to ≤12 years, and ≥13 to ≤18 years)
- Achenbach CBCL (4 to 5 years, 6 to 18 years)
- BRIEF-P/BRIEF (4 to <5 years, ≥5 years).

4.9 Stratum Pooling

The stratification factors for this study are Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analyses will use the stratification factors from IRT.

To determine if strata pooling should occur for time to event (2nd PGTCS) analysis:

For the subjects with Baseline PGTCS frequency ≤2 per 28 days, the events for each of the 3 age at informed consent categories will be summed. For categories with < 3 total events, the combining should occur as follows:

- If 2 of the age at informed consent categories combined have < 3 total events, then all age categories are combined for the analysis.
- If ≥4 to <12 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥12 and <18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the strata with the 2nd smallest number of events.

Repeat the algorithm for combining strata for the subjects who did not have events if there are categories with < 3 total non-events.

For the subjects with Baseline PGTCS frequency >2 per 28 days, repeat the same exercise to determine stratum pooling for both events and non-events.

For each primary efficacy endpoint sensitivity analysis which uses stratum pooling, the pooling of the strata should be reassessed since the event distribution for the specific sensitivity may be different than the distribution in the primary efficacy endpoint analysis.

Time to 1st PGTCS analyses:

The prior algorithm for stratum pooling will be used to determine stratum pooling, except that "events" will now be in reference to subjects having only 1 PGTCS.

Seizure freedom analyses:

The prior algorithm for stratum pooling will be used to determine stratum pooling, except that "events" will now be in reference to subjects having 0 PGTCS.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects screened and the number and percentage of screen failures will be summarized overall. Screen failures are those subjects who are in the ScS and either met an exclusion criterion or did not meet an inclusion criterion. The reason for screen failure will be presented. The number and percentage of baseline failures due to PGTCS frequency during the Combined Baseline Period will also be summarized. The study eligibility criteria and those

subjects who did not meet it will be listed. All disposition data for the ScS will be presented in subject data listings.

The number of subjects in the ScS, Randomized Set (RS), SS, FAS, and PPS will be presented by investigator; the date of first subject in and date of last subject out will also be included in this summary. The subject populations will be listed.

The overall number and percentage of subjects who completed and discontinued from the study will be presented for the SS, FAS, and PPS including number and percentages for each reason for discontinuation. The completion of the study is defined as meeting any of the predetermined exit criteria (including when the 125th event has occurred) or experiencing <2 PGTCS within the 24-week treatment period. Discontinuation is defined as the completion of the ET Visit in all other cases. This summary will be repeated for specific subgroups as detailed in Section 4.8 for the SS and FAS. The study termination information will be presented in the subject data listings.

A by-subject listing will be presented to show all visit dates and the associated relative day.

5.2 Protocol deviations

The number and percentage of subjects without any important protocol deviations and with at least 1 important protocol deviation in each of the categories defined in the prior to database lock and unblinding will be summarized overall for the RS.

All important protocol deviations for subjects in the RS will be listed by site, subject number, and protocol deviation category.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, demographics and baseline characteristics will be summarized by treatment group and overall.

6.1 Demographics

6.1.1 Derivation of demographics variables

6.1.1.1 BMI

The body mass index (BMI) will be derived at Baseline only, from the Baseline height and weight values. BMI will be calculated using the following formula:

$$\text{BMI}\ (\text{kg/m}^2) = 10000 * \frac{\text{weight}\ \ (\text{kg})}{[\text{height}\ \ (\text{cm})]^2}$$

6.1.2 Analysis of demographics variables

Baseline demographics will be summarized for the SS and include gender, race, ethnicity, age, age category, age strata from IRT, height (cm), weight (kg), BMI (kg/m^2). Note age from the CRF will be summarized.

Demographics will be listed for all subjects screened.

6.2 Other Baseline characteristics

6.2.1 Derivation of other Baseline characteristics

6.2.1.1 Time since first diagnosis

The time since first diagnosis of epilepsy is calculated as follows:

the date of informed consent – the date of first epilepsy diagnosis/365.25.

Imputation for partial dates of first epilepsy diagnosis will be imputed as described in Section 4.2.2.

6.2.1.2 Age at diagnosis

Age at diagnosis of epilepsy will be calculated using the first epilepsy diagnosis date and the date of birth. Imputation for partial dates of first epilepsy diagnosis will be imputed as described in Section 4.2.2.

6.2.2 Analysis of other Baseline characteristics

Combined Baseline PGTCS frequency, 12-week Historical Baseline PGTCS frequency, and 4-week Prospective Baseline PGTCS frequency derived as frequencies per 28 days will be summarized as continuous data. Combined Baseline PGTCS frequency will also be summarized as categorical data (≤2 per 28 days and >2 per 28 days) from the CRF and IRT at randomization.

The following Baseline characteristics will also be presented:

- Time since first diagnosis at date of consent
- Age at diagnosis of epilepsy
- Number of lifetime AEDs and Benzodiazepines (0, 1-3, 4-6, ≥7)
- Concomitant benzodiazepine use at study entry (yes, no)
- ILAE (1989) Seizure classification history
- Classification of epileptic syndrome
- Etiology of epilepsy

All Baseline characteristics will be presented in data listings. All reproductive potential and birth control information will be presented in data listings.

6.3 Subgroups

All subgroups detailed in Section 4.8 will be summarized in a table for the SS and FAS. Subgroup identification will also be listed.

6.4 Medical history and concomitant diseases

Previous and ongoing medical history conditions will be summarized by system organ class (SOC) and preferred term (PT) for the SS. A similar summary will be provided for concomitant diseases for the SS. Concomitant diseases are medical history events which are ongoing at the Screening Visit.

The data, including the SOC, PT and verbatim reported term, will also be presented in data listings. A glossary of medical history SOC and PTs will also be completed.

6.5 Procedure history

All procedure history will be presented in data listings.

6.6 Prior and concomitant medications

Medications with a start date before the first dose of study medication will be considered prior medications. Medications taken on or after the date of the first dose of study medication will be considered concomitant medications. 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 concomitant. Medications with a missing start date whose stop date is prior to the date of the first dose of study medication will be considered as prior medications.

Details regarding imputation of incomplete dates are described in Section 4.2.3.

Medications will be summarized using the Anatomical Therapeutic Chemical (ATC) codes from the WHO-DD. All tabulations will be sorted by frequency of the higher-level ATC code and by frequency of the lower level ATC code within the higher-level ATC code.

Medications (excluding AEDs and benzodiazepines) will be summarized separately for prior and concomitant medications by ATC level 1 (anatomical main group) and ATC level 2 (therapeutic subgroup) for the SS.

Lifetime AEDs and benzodiazepines will be summarized separately by ATC level 4 (chemical subgroup) and PT for the SS. AEDs and benzodiazepines at study entry will also be summarized separately by ATC level 4 and PT for the SS.

Concomitant AEDs will be defined by a manual medical review of all unique ATC codes and indications reported in the database to identify medications taken to treat epilepsy. Concomitant AEDs and benzodiazepines taken for any epilepsy indication during the Treatment Period will be summarized separately by ATC level 4 and PT for the SS.

A glossary of ATC codes and associated investigator's terms for all AEDs or benzodiazepines and all other medications (excluding AEDs and benzodiazepines) will be listed separately in data listings. The WHO-DD coding and other information for AEDs or benzodiazepines and all other medications (excluding AEDS and benzodiazepines) will be listed separately in subject data listings. AEDs flagged as rescue medications will also be listed in subject data listings.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance data will be included in subject data listings.

8 EFFICACY ANALYSES

Most efficacy analyses will be performed using the FAS population; in other cases, the population will be stated.

For primary efficacy endpoint analyses, only data up to and including the day of the event, the Visit 10 date, last Treatment Period dose date, Day 166 or the date of the 125th event, whichever is earlier, will be included. For the secondary efficacy endpoint analyses, only data up to and including the day of the first PGTCS, the Visit 10 date, the last Treatment Period dose date, Day 166 or the date of the 125th event, whichever is earlier, will be included. For all other exploratory efficacy variables, all appropriate seizure data during the Treatment Period, will be included. All seizure diary data will be listed including data not included in efficacy analyses.

Testing for the primary efficacy endpoint will be done at the 5% level (2-sided). Provided that the primary efficacy endpoint is statistically significant, a gatekeeping strategy will be used to test the key secondary efficacy variable, seizure freedom. No additional adjustments for multiplicity are required as all additional inferences will be hypothesis-generating only.

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Derivations of primary efficacy variable

For the primary efficacy variable, an event and how time to event is calculated is described in Section 3.2.3, keeping in mind Section 3.2.2. Censoring of subjects for this analysis will be as described in Section 3.2.4 . If a day is marked in the CRF as "not done", it will be assumed that no seizures occurred on that day.

8.1.2 Primary analysis of the primary efficacy variable

The primary efficacy variable, time to event during the 166-day Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT and pooled as described in Section 4.9.

The hypothesis for the assessment of primary efficacy variable (time to event) is as follows:

$$H_0: \beta=0$$

Versus

$$H_1: \beta\neq0$$

where β is the coefficient of an independent variable representing the treatment effect in the model. The hazard function is represented by

$$h(t,X) = h_0(t)\exp(\sum_{j=1}^{p}\beta_j X_j)$$

where x_j is the collection of independent variables and $h_0(t)$ is the baseline hazard at time t. For the null hypothesis, the testing will be 2-sided with an α=0.05; the p-value will be presented. The

assumptions of proportional hazards will also be assessed graphically (e.g. log (log S) plot vs time, empirical score process) for any departure; non-proportionality is not expected when using a stratified Cox model. Depending on the departure from proportional hazards, a sensitivity analysis (e.g. piecewise proportional hazards, time-varying coefficient, restricted mean survival) may be performed.

The stratified hazard ratio (HR) will be calculated using the placebo arm as the reference group. The 95% CI for the HR will also be reported.

Additionally, a Kaplan-Meier (KM) plot for time to event as well as the KM estimate for the median time to event and 95% CI will be provided. If the median time is not estimable, then the 25th percentile and 95% CI will be provided. The number of events will be reported by treatment group for the Titration Period, first 12 Weeks, and Treatment Period as well as the % of subjects who were censored in the analysis.

8.1.3 Secondary analyses of the primary efficacy variable

The summary of time to the event during the 166-day Treatment Period will be presented by all subgroup for the FAS. A KM plot for time to second PGTCS by all subgroups will also be provided.

8.1.4 Supportive and sensitivity analyses of the primary efficacy variable

The following additional sensitivity analyses on the primary efficacy endpoint will be conducted in order to assess the effect of dropouts, important protocol deviations, and operational bias on the primary endpoint:

- Repeat the primary efficacy analysis using the PPS.
- Repeat the primary efficacy analysis using all PGTCS data (ie, all reported events after the date of the 125th event) through each subject's first 166 days of treatment, on the FAS.
- Repeat the primary efficacy analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy, consent withdrawn, or lost to follow-up will be analyzed as treatment failures (ie, events at the time of discontinuation).
- Repeat the primary efficacy analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy or AEs only will be analyzed as treatment failures.
- Repeat the primary efficacy analysis using the FAS, comparing the event rates prior to vs after each interim analysis to examine possible operational bias due to unblinding.
- Repeat the primary efficacy analysis using the FAS, except all subjects who prematurely discontinue after their 1st PGTCS will be analyzed as treatment failures.

8.2 Statistical analysis of the secondary efficacy variables

Provided that the primary efficacy endpoint is statistically significant, a gatekeeping strategy will be used to test the key secondary efficacy variable. Analyses of all other secondary efficacy variables will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary efficacy analysis of the primary efficacy variable (as described in Section 8.1.2) and the analysis of the key secondary efficacy variable will be exploratory only.

8.2.1 Derivations of secondary efficacy variables

8.2.1.1 Variable: Seizure freedom for PGTCS for the 166-day Treatment Period

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary and PGTCS were assessed. Days in the seizure diary which are marked as "not done" on the CRF will be counted as seizure-free days from PGTCS.

A subject will have seizure freedom from PGTCS for the 166-day Treatment Period if the subject completed the Treatment Period and reported zero PGTCS or "not done" for all days during the 166-day Treatment Period. Ongoing subjects who are seizure-free from PGTCS on the date of the 125th event do not have seizure-freedom from PGTCS unless they are seizure-free from PGTCS for 166 days.

8.2.1.2 Variable: Time to first PGTCS during the 166-day Treatment Period

For PGTCS, how the time to first PGTCS is calculated is described in Section 3.2.3. Censoring of subjects for this analysis will be as described in Section 3.2.4 .

If a day is marked in the CRF as "not done", it will be assumed that no seizures occurred on that seizure diary day.

8.2.2 Analysis of secondary efficacy variables

Analyses of secondary efficacy variables will be performed for the FAS.

8.2.2.1 Analysis: Seizure freedom for PGTCS for the 166-day Treatment Period

Analysis of the key secondary efficacy variable, seizure freedom for PGTCS for the 166-day Treatment Period, will be evaluated using an extended Mantel-Haenszel testing procedure which takes into account that the subjects were initially stratified for the subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT and pooled as described in Section 4.9.

The hypothesis for the assessment of the key secondary efficacy (PGTC seizure-freedom) is as follows:

$$H_0: S(t{=}166)_{LCM} = S(t{=}166)_{PBO}$$

Versus

$$H_1: S(t{=}166)_{LCM} \neq S(t{=}166)_{PBO}$$

Where $S(t{=}166)$ is the cumulative rate of subjects remaining seizure-free from PGTCS for 166 days.

Estimation of treatment difference:

KM methods will be used to estimate the proportion of subjects remaining seizure-free from PGTCS at Day 166. The estimate for the difference in Day 166 seizure-freedom from PGTCS will be adjusted for subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The estimate for the stratified difference in proportion of

subjects who are seizure-free from PGTCS on LCM vs PBO and a corresponding 95% two-sided confidence interval ($CI_{LCM-PBO}$) will be produced using mantel Haenszel methods (LaVange et al, 2005). The statistical methodology is expressed as follows:

$d=\sum_{h=1}^{6} w_h(S_{h1}-S_{h2})$

Where S_{hi}=KM estimate of 166-day seizure freedom from PGTCS for treatment i (1=LCM and 2=PBO) in stratum h (1= ≤2 per 28 days Baseline PGTCS frequency and ≥ 4 to <12 years of age, 2= ≤2 per 28 days Baseline PGTCS frequency and ≥12 to <18 years of age, 3= =≤2 per 28 days Baseline PGTCS frequency and ≥18 years of age, 4= >2 per 28 days Baseline PGTCS frequency and ≥ 4 to <12 years of age, 5= >2 per 28 days Baseline PGTCS frequency and ≥12 to <18 years of age and 6= >2 per 28 days Baseline PGTCS frequency and ≥18 years of age and $w_h=\{(n_{h1}*n_{h2})/(n_{h1}+n_{h2})\}/\sum_{h=1}^{6}\{(n_{h1}*n_{h2})/(n_{h1}+n_{h2})\}\}$

where n_{hi} is the number of subjects in I treatment group and stratum h. The variance of d is calculated as $Var(d)=\sum_{h=1}^{6} w_h^2\{Var(S_{h1})+Var(S_{h2})\}$ where $Var(S_{h1})$ and $Var(S_{h2})$ are the Greenwood estimates of variance for S_{h1} and S_{h2}.

The stratified proportion of subjects remaining seizure free from PGTCS for at least 166 days in each treatment group and the associated variance are derived as follows using Mantel Haneszel methods:

The KM estimate for the LCM 166-day seizure-freedom from PGTCS rate is calculated as $S_1=\sum_{h=1}^{6} w_h S_{h1}$

The KM estimate for the PBO 166-day seizure-freedom from PGTCS rate is calculated as $S_2=\sum_{h=1}^{6} w_h S_{h2}$

The variance is S1 is calculated as $Var(S_1)=\sum_{h=1}^{6} w_h^6 Var(S_{h1})$

The variance of S2 is calculated as $Var(S_2)=\sum_{h=1}^{6} w_h^6 Var(S_{h2})$

In order to assess superiority, 2-sided testing with α=0.05 will be used. The superiority test statistic, $Q=d^2/Var(d)$ will be assessed by a chi-square distribution with 1 degree of freedom. This statistic is referred to as the "row mean score statistic" when using Proc Freq.

The number and percentage of subjects who experience a PGTCS or censoring and the KM seizure-free rate from PGTCS (and 2-sided 95% CI) by Day 166 will be presented by treatment group for each stratum and overall. The stratified seizure-freedom rate from PGTCS (and 2-sided 95% CI) at Day 166 for each treatment group and the difference between treatment groups will be presented. A Kaplan-Meier plot will be presented by treatment group for each stratum and overall.

For the gatekeeping strategy, if the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

8.2.2.2 Analysis: Time to first PGTCS during the 166-day Treatment Period

Time to the first PGTCS during the 24-week Treatment Period will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined

Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT and pooled as described in Section 4.9.

The hypothesis for the assessment of the time to first PGTCS is as follows:

$$H_0: \beta=0$$

Versus

$$H_1: \beta\neq0$$

where β is the coefficient of an independent variable representing the treatment effect in the model. The hazard function is represented by

$$h(t,X) = h_0(t)\exp(\sum_{j=1}^{p}\beta_j X_j)$$

where x_j is the collection of independent variables and $h_0(t)$ is the baseline hazard at time t. For the null hypothesis, the testing will be 2-sided with an α=0.05. The assumptions of proportional hazards will also be checked using the same approach as for the primary efficacy endpoint.

The stratified HR will be calculated using the placebo arm as the reference group. The 95% CI for the HR will also be reported.

Additionally, a KM plot for time to 1st PGTCS as well as the KM estimate for the median time to 1st PGTCS and 95% CI will be provided. If the median time is not estimable, then the 25th percentile and 95% CI will be provided. The number of 1st PGTCS will be reported by treatment group for the Titration Period, first 12 Weeks, and Treatment Period as well as the % of subjects who were censored.

8.3 Analysis of seizure related other efficacy variables

All seizure data recorded during the treatment period will be summarized and listed for the seizure related other efficacy variables. Analyses of seizure-related other efficacy variables will be performed for the FAS. For absence seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of absence seizures or reported absence seizures during baseline or the 24-week treatment period. For myoclonic seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of myoclonic seizures or reported myoclonic seizures during baseline or the 24-week treatment period.

8.3.1 Derivations of seizure related other efficacy variables

8.3.1.1 Variable: PGTCS frequency per 28 days

In order to account for potential differences in the durations of the study periods for individuals, PGTCS data will be normalized to 28 days.

The 28-day PGTCS frequency (SF) will be calculated for the Combined Baseline and Treatment Periods as:

SF =

(# PGTCS in the relative period/# days in relative period with evaluable PGTCS data)*28

The percent change (PCH) in PGTCS frequency per 28 days from the Combined Baseline (CB) to the appropriate analysis period (T) is defined as:

PCH = [(SFT – SFCB) / SFCB] x 100

where SFT corresponds to the 28-day PGTCS frequency during the relative period and SFCB corresponds to the 28-day Combined Baseline PGTCS frequency. PCH is calculated for 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

8.3.1.2 Variable: Days with seizures per 28 days

The number of days with absence seizures per 28 days will be calculated separately for the Prospective Baseline and the Treatment Period as:

D = ([# days with absence seizures in the relative period] / [# days in relative period with evaluable seizure data]) * 28.

Similarly, the number of days with myoclonic seizures per 28 days will be calculated.

The percent change (PCH) in days with absence seizures per 28 days from the Prospective Baseline (B) to the appropriate analysis period (T) is defined as:

PCH = [(DT – DB) / DB] x 100

where DT corresponds to the number of days with absence seizures per 28 days during the relative period and DB corresponds to the number of days with absence seizures per 28 days during the Prospective Baseline Period. If DB is zero, then PCH will be missing and any such subjects will be excluded from the percent change summary. PCH will be calculated for the 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

Similarly, the percent change in the number of days with myoclonic seizures per 28 days from the Prospective Baseline Period will be calculated.

8.3.1.3 Variable: Seizure-free status

A subject will have seizure-free status for PGTCS=yes for the Treatment Period if the subject completed the Treatment Period (with a minimum 166 days) and reported zero PGTCS or "not done" for all days during the Treatment Period. If the subject is exited from the study due to the 125th event occurring reporting zero PGTCS or "not done" for all days and duration of the Treatment Period is < 166 days, then the subject has not achieved seizure-free status for PGTCS.

A subject will have seizure free status=yes for all generalized seizure types for the applicable Treatment Period if the subject completed the Treatment Period and reported zero generalized seizures for all days during the Treatment Period when the number of generalized seizures was available, and had <10% of days during the Treatment Period with seizure data reported as "not done".

Seizure-free statuses will be calculated for 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

8.3.1.4 Variable: Responder status – reduction in PGTCS frequency

Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.3.1.1 . A 50% responder is defined as a subject experiencing ≥50%

reduction in PGTCS frequency per 28 days from the Combined Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in PGTCS frequency per 28 days from Combined Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

8.3.1.5 Variable: PGTCS frequency - worsening

Seizure worsening is defined as a subject experiencing ≥50% increase in PGTCS frequency per 28 days from Combined Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

8.3.1.6 Variable: Responder status – reduction in days with absence seizures

Response to treatment for absence seizures per 28 days will be based on the percent change in days with absence seizures, calculated as described in Section 8.3.1.2. A 50% responder is defined as a subject experiencing ≥50% reduction in days with absence seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in days with absence seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

8.3.1.7 Variable: Responder status – reduction in days with myoclonic seizures

Response to treatment for myoclonic seizures per 28 days will be based on the percent change in days with myoclonic seizures, calculated as described in Section 8.3.1.2. A 50% responder is defined as a subject experiencing ≥50% reduction in days with myoclonic seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in days with myoclonic seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

8.3.1.8 Variable: Days with absence and myoclonic seizures – worsening

Safety of the LCM treatment will be based on the percent change in days with absence seizure per 28 days and days with myoclonic seizure per 28 days. The increase in days with absence seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period. The increase in days with myoclonic seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period.

8.3.1.9 Variable: Absence and myoclonic seizure frequencies per 28 days

In order to account for potential differences in the durations of the study periods for individuals, absence and myoclonic seizure data will be normalized to 28 days.

The 28-day absence SF will be calculated for the Prospective Baseline and Treatment Periods as:

SF =

(# absence seizures in the relative period/# days in relative period with evaluable absence seizure data)*28

The PCH in Absence seizure frequency per 28 days from the Prospective Baseline (PB) to the appropriate analysis period (T) is defined as:

PCH = [(SFT – SFPB) / SFPB] x 100

where SFT corresponds to the 28-day absence seizure frequency during the relative period and SFPB corresponds to the 28-day Prospective Baseline absence frequency; if subjects had no absence seizures in Prospective Baseline, then PCH cannot be calculated. PCH is calculated for 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

SF and PCH are calculated for subjects with myoclonic seizures using the same algorithm described above.

8.3.1.10 Variable: Responder status – reduction in absence and myoclonic seizure frequencies

Response to treatment will be based on the percent change in absence and myoclonic seizure frequencies, calculated as described in Section 8.3.1.9. A 50% responder is defined as a subject experiencing ≥50% reduction in absence (or myoclonic) seizure frequency per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in absence (or myoclonic) seizure frequency per 28 days from Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

8.3.1.11 Variable: Absence and myoclonic seizure frequency - worsening

Safety of the LCM treatment will be based on the percent change in absence seizure frequency per 28 days and myoclonic seizure frequency per 28 days. The increase in absence seizure frequency per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period. The increase in myoclonic seizure frequency per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period.

8.3.2 Analysis of seizure related other efficacy variables

8.3.2.1 Analysis: Percent change in PGTCS frequency per 28 days from Combined Baseline

Descriptive statistics will be provided on the percent change in PGTCS frequency for the first 6 weeks of (entire Titration Period), first 12 weeks of, and the entire Treatment Period.

All PGTCS frequency per 28 days data will be listed.

8.3.2.2 Analysis: Reduction in days with seizures per 28 days

The following data will be summarized with descriptive statistics only:

- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline

- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 12 weeks of the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 12 weeks of the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

All seizure days data for absence and myoclonic seizures will be listed.

8.3.2.3 Analysis: Seizure-free status

The following seizure-free status (yes/no) summaries will be provided:

- Seizure-free status (yes, no) for PGTCS for the first 6 weeks of the Treatment Period (Titration Period)
- Seizure-free status (yes, no) for PGTCS for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTCS for the 24-week Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the first 6 weeks of the Treatment Period (Titration Period)
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period

8.3.2.4 Analysis: Responder status – reduction in PGTCS frequency

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the first 6 weeks (Titration Period) compared to the Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the first 12 weeks of the Treatment Period compared to the Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the Treatment Period compared to the Combined Baseline

- Percentage of subjects with at least a 75% reduction in PGTCS frequency during the first 6 weeks (Titration Period) compared to the Combined Baseline
- Percentage of subjects with at least a 75% reduction in PGTCS frequency during the first 12 weeks of the Treatment Period compared to the Combined Baseline
- Percentage of subjects with at least a 75% reduction in PGTCS frequency during the Treatment Period compared to the Combined Baseline

A histogram of ≥50%, ≥75%, and 100% (seizure freedom) responder status for PGTCS frequency during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

8.3.2.5 Analysis: Responder status – reduction in days with absence seizures

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in absence seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure days during the Treatment Period compared to the Prospective Baseline
- A histogram of ≥50% and ≥75% responder status for reduction in days with absence seizures during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

8.3.2.6 Analysis: Responder status – reduction in days with myoclonic seizures

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in myoclonic seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days during the Treatment Period compared to the Prospective Baseline

- Percentage of subjects with at least a 75% reduction in myoclonic seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure days during the Treatment Period compared to the Prospective Baseline
- A histogram of ≥50% and ≥75% responder status for reduction in days with myoclonic seizures during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

8.3.2.7 Analysis: Percent change in absence and myoclonic seizure frequency per 28 days from Prospective Baseline

Descriptive statistics will be provided on the percent change in absence and myoclonic seizure frequencies for the first 6 weeks of (entire Titration Period), first 12 weeks of, and the entire Treatment Period.

All absence and myoclonic seizure frequency per 28 days data will be listed.

8.3.2.8 Analysis: Responder status – reduction in absence and myoclonic seizure frequency

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in absence seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure frequency during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure frequency during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline

- Percentage of subjects with at least a 75% reduction in myoclonic seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure frequency during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure frequency during the Treatment Period compared to the Prospective Baseline

8.4 Analysis of health outcome other efficacy variables

8.4.1 Derivations of health outcome other efficacy variables

8.4.1.1 QOLIE-31-P variables

The Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) Version 2 will be used to evaluate the health-related quality of life (HRQoL) of study subjects ≥18 years of age.

The QOLIE‑31‑P total score, subscale scores, and health status item score are calculated according to the scoring algorithm defined in Section 12.1 which accounts for the possibility of missing values. Scores range from 0 to 100 and higher scores indicating better functioning. QOLIE- 31-P data that are completely missing will not be replaced.

Subscale scores

As a first step to calculating the subscale scores, the individual responses for the 30 subscale items are rescaled to a 0 to 100 scale with higher scores reflecting better functioning; the rescaled values for each item are defined in Section 12.1. Each subscale score is then calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Total score

Total score is calculated as a weighted sum of the subscale scores based on the weighting in Section 12.1. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

Health status item

The response for the health status item is a multiple of 10 ranging from 0 to 100 with a higher score corresponding to a better health status. The health status item response is analyzed without rescaling.

Distress items

Each subscale includes 1 distress item. The response for each distress item is an integer ranging from 1 to 5. The response for each distress item will be converted to a 0 to 100 scale (ie, 0, 25, 50, 75, and 100) with a higher score corresponding to greater distress.

Prioritization item

The response for each subscale for the prioritization item is an integer ranging from 1 to 7. The prioritization ranking is analyzed without rescaling.

8.4.1.2 PedsQL variables

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations (<18 years), including those with acute or chronic health conditions.

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 – (response x 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) for each subject. To create the Total Scale Score, the mean is computed over the number of items answered on all the Scales

8.4.1.3 EQ-5D-3L quality of life variables

The 3-Level EuroQol-5 Dimensional Quality of Life Assessment (EQ-5D-3L) is a self-administered questionnaire designed to measure health status in subjects ≥12 years of age.

The EQ-5D-3L defines health in terms of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is divided into 3 levels:

- No problem=1
- Some or moderate problems=2
- Extreme problems=3

The EQ-5D-3L also captures a self-rating of health status on a 20cm vertical visual analog scale, anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

At each time point, an EQ-5D-3L utility value will be mapped to each subject's health state. Health state is derived from the subject's numerical ratings of the 5 EQ-5D-3L Dimensions. The order of the ratings is Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression. Health state is derived by concatenating the numerical ratings of the 5 dimensions. For example, a health state may be derived as 11111, indicating best possible health.

A utility value will then be mapped to the derived health states, using the UK EQ-5D-3L value set. This set is available to Global Statistical Programming in excel format.

The mapped utility values will make up the utility variable.

8.4.1.4 Hospital stays

An event logged on the Hospitalization/Emergency Room (ER) Visit form of the eCRF where "Emergency room" is marked as initial entry point will be defined as an ER visit. An ER visit with a subject transfer to an inpatient general ward will also be counted as a hospitalization.

However, all other instances of ER visits (where subject transfer is not to an inpatient general ward) will not be counted as hospitalizations.

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

8.4.2 Analysis of health outcome other efficacy variables

8.4.2.1 QOLIE-31-P variables

QOLIE-31-P data, for a specific visit may have a status of Abandoned if the subject doesn't complete the questionnaire. If the subject has duplicate QOLIE-31-P data for the same visit, where one record is deemed as Abandoned and one record is deemed as Completed, the Completed data will be used in the analysis and not the Abandoned record. All recorded QOLIE-31-P data will be listed.

The observed values and change from Baseline will be summarized descriptively for the total score, the subscale scores, health score and the distress items for each visit and Last Visit. The mean observed values for the prioritization items will laso be summarized for each visit and Last Visit. They will all be summarized for both Visit 10 and Visit 10/ET. The scores for individual subscales will only be analyzed when a total score can be calculated (ie, all subscales have a non-missing score). Individual questions will not be summarized. Individual questions, subscale scores, and total scores will be presented in subject data listings. The means of the QOLIE-31-P total score, subscale scores and health status item score will be plotted by visit.

8.4.2.2 PedsQL variables

The observed 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. They will be summarized for both Visit 10 and Visit 10/ET. Subgroup summaries by age will be performed using the age groupings for which different questionnaires were entered: 4 years, ≥5 to ≤7 years, ≥8 to ≤12 years, and ≥13 to ≤18 years.

All PedsQL data will be listed. The means of the PedsQL subscale scores and total score will be plotted by visit.

8.4.2.3 EQ-5D-3L quality of life variables

The observed values for each dimension and the mapped utility values will be summarized for each visit and Last Visit. They will be summarized for both Visit 10 and Visit 10/ET.

Observed values and the change from Baseline for the VAS score for general health state will also be summarized.

All EQ-5D-3L data will be presented in subject data listings. The mean of the EQ-5D-3L VAS will be plotted by visit. For the EQ-5D-3L, the percentage of subjects reporting a level within each dimension will be plotted in a histogram.

8.4.2.4 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. Additionally, subjects who had any procedures or surgeries prior to study entry based on the Procedure History eCRF will also be listed.

8.4.2.5 Healthcare provider consultations

All healthcare provider consultations data will be listed.

8.4.2.6 Hospital stays

All hospitalization/ER data will be listed.

8.4.2.7 Number of working or school days lost due to epilepsy

All working or school days lost data will be listed.

8.4.2.8 Number of days with help from a paid caregiver due to epilepsy

All data regarding help from a paid caregiver will be listed.

8.4.2.9 Socio-professional data

The number and percentage of subjects by each response level for highest level of education, housing status, current professional status, regular assistance in usual activities, and driving status will be summarized for each visit and Last Visit for the FAS. Percentages will be relative to the number of subjects with a response to each item. No statistical comparisons will be carried out for socio-professional data.

All socio-professional data will be listed.

9 PHARMACOKINETICS

LCM plasma concentration will be summarized using the SS. Descriptive statistics of LCM plasma concentrations will be presented by visit and actual dose. The actual dose is defined as the most recent dose administrated prior to PK sampling.

The following parameters will be calculated for each of the sampling points: n, nLOQ (number of measurements above or equal to the lower limit of quantification [LOQ]), arithmetic mean, standard deviation (SD) and coefficient of variation (CV), median, minimum, and maximum value.

Values below LOQ will be replaced by 0 in calculations of mean, SD, CV(%) and median. Mean, SD and CV(%) will only be calculated if at least 2/3 of the data are above LOQ at the respective time point. In tables showing mean values, where values below LOQ are included in the calculation of mean values, these mean values will be marked.

A listing of LCM plasma concentration data by subject and visit will include actual doses, date and time of the most recent administration, date and time of sampling, time interval between

plasma sample and the most recent administration (in hours), visit, relative day, and the kit number. Samples that were excluded from the descriptive statistics will be marked in the listing.

10 SAFETY ANALYSES

10.1 Extent of exposure

10.1.1 Derivation of exposure variables

Study medication treatment duration will be calculated as ([last study medication dose during the Treatment Period – first study medication dose] + 1 day). Subject-years of exposure is the total treatment duration in days divided by 365.25.

The mean exposure per day for an analysis period is calculated as the total exposure in milligrams during the analysis period (based on the randomized treatment group or protocol defined treatment regimen incorporating any scheduled dose changes) divided by the duration of exposure (days). Days during an analysis period with unknown dosing are to be excluded from both the numerator and the denominator for the calculation of mean exposure per day.

10.1.2 Analysis of exposure variables

Total duration of exposure (days) for each treatment group during the Titration Period, Maintenance Period, and Treatment Period will be summarized by region for the SS using descriptive statistics. The number of days of exposure in the Treatment Period will be calculated as the last dose date minus the first dose date +1. Study medication taken during the Taper and Transition Periods will not be included in these calculations.

Treatment duration will be summarized with the number and percentage of subjects with treatment duration by 3 Week categories: 1 to 21 days, 22 to 42 days, 43 to 63 days, 64 to 84 days, 85 to 105 days, 106 to 126 days, 127 to 147 days, 148 to 168 days, and > 168 days. Furthermore, the subject years exposed will be presented for the entire Treatment Period.

If actual dosing information is presented, the LCM dose categories for oral solution are as follows: 0mg/kg/day/Unknown, >0 to <4mg/kg/day, ≥4mg/kg/day to <8mg/kg/day, and ≥8mg/kg day. The LCM dose categories for tablets are as follows: 0mg/day/Unknown, >0 to <200mg/day, ≥200 to <400mg/day, ≥400 to <600mg/day, ≥600 to 800mg/day, and ≥800mg/day.

The mean dose per day will be presented for the 3 different weight categories: <30kg (mg/kg/day), ≥30kg to <50kg (mg/kg/day) and ≥50kg (mg/day).

This analysis will be repeated for each subgroup as detailed in Section 4.8.

Detailed LCM exposure, LCM dosing, and drug accountability will be presented in subject data listings.

10.2 Adverse events

Adverse events will be coded using MedDRA, and tabulated by SOC and PT for each treatment group for the SS and will include the number and percentage of subjects experiencing each event at least once. All summaries will be sorted alphabetically by SOC and by frequency of events within each SOC, starting with the most frequent event for the LCM arm.

Adverse events will be considered treatment-emergent if the event had onset on or after the date of the first study medication dose and within 30 days following the last study medication dose or

events whose intensity worsened on or after the date of first study medication dose and within 30 days following the date of last study medication administration.

If the last dose of study medication administration is unknown, any event occurring after the first study medication dose will be considered treatment-emergent. If the start date of an AE is completely missing and the stop date is either unknown or after the date of the first dose of study medication, the AE will be considered as treatment-emergent. Incomplete dates for AEs will be handled as described in Section 4.2.3.

Treatment emergent adverse events (TEAEs) during the Treatment Period, Maintenance Period and Taper/Safety Follow-Up Period, respectively, are TEAEs with an onset date during the respective period.

The following summaries will be presented by randomized treatment group:

- Overview of TEAEs
- Overview of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs
- Incidence of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs in the Titration Period
- Incidence of TEAEs in the Maintenance Period
- Incidence of TEAEs in the Taper Period
- Incidence of TEAEs in the Transition Period
- Incidence of TEAEs by intensity
- Incidence of common TEAEs for US labeling (above or equal to reporting threshold of 2% (prior to rounding) of subjects in the total LCM group)
- Incidence of common drug-associated TEAEs (TEAEs occurring in ≥5% of subjects in the LCM group and occurring twice as often as in the placebo group)
- Incidence of common TEAEs for EU labeling (above or equal to reporting threshold of 1% (prior to rounding) of subjects in the total LCM group) and occurring >1% than in the placebo group
- Incidence of serious TEAEs
- Incidence of serious TEAEs – Subject numbers
- Incidence of TEAEs leading to discontinuation
- Incidence in TEAEs leading to discontinuation in the Titration Period
- Incidence in TEAEs leading to discontinuation in the Maintenance Period
- Incidence in TEAEs leading to discontinuation – Subject numbers
- Incidence of other significant TEAEs (See Section 12.2.1 for details)

- Incidence of TEAEs for potential drug-induced liver injury (PDILI) (See Section 12.2.2 for details)

To assess TEAEs related to epilepsy, PTs will be identified by ongoing manual medical review. The following PTs (including those identified from continuing medical review) will be summarized: petit mal epilepsy, myoclonus, and myoclonic epilepsy.

- Incidence of TEAEs related to epilepsy by 3-month exposure period of TEAE onset

The dose at onset TEAE summaries will be presented by the LCM dosing categories presented in Section 10.1.2. AEs of unknown dosing are those with no known dose or known dosing and partial AE start or stop dates.

- Incidence of TEAEs by actual dose at onset

Subject data listings will be presented for the following:

- Subjects experiencing adverse events on the ES
- Subjects experiencing Serious TEAEs on the SS
- Subjects experiencing TEAEs leading to discontinuation on the SS

A glossary of AEs will be presented showing the mapping of investigator terms to coded SOC and PTs.

A list of further AE tables required for EudraCT and clinicaltrials.gov is provided in Section 12.5.

10.3 Clinical laboratory evaluations

Measurement and change from Baseline in continuous laboratory parameters, including hematology, clinical chemistry, endocrinology, and urinalysis will be summarized using descriptive statistics for the scheduled visits. When analyzing categorical data, the number and percentage of subjects in each category will be presented. In addition, summary statistics for the actual value and change from Baseline will be presented for Last Visit, minimum, and maximum post-Baseline values obtained during the Treatment Period. Repeated or unscheduled laboratory assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period.

Shifts based on the normal range (ie, low, normal, high, and missing) for each hematology and clinical chemistry lab parameter will be presented by maximum value during the Treatment Period relative to Baseline by treatment group. Similar shift tables for Baseline versus minimum value during the Treatment Period will also be presented. Unscheduled visits will be considered when determining the maximum and minimum value during the defined treatment period.

Treatment-emergent markedly abnormal (TEMA) values indicate significant deviations from the expected range of age-appropriate values. TEMA laboratory abnormalities results are those that are observed post-Baseline during the Treatment Period but are not present at Baseline. TEMA values for serum chemistry and hematology laboratory parameters are provided in UCB conventional (traditional) and standard units. The definition of MA values for hematology and chemistry values can be found in Section 12.3. The number and percentage of subjects with at

least 1 TEMA value will be summarized by scheduled visit, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified. TEMA values are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period.

A table summarizing the number of subjects meeting the potential drug induced liver injury criteria will also be presented.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC) can be found in Section 12.4. The number and percentage of subjects with treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher (hematology and clinical chemistry) will be summarized by treatment group, laboratory parameter, and visit for the Treatment Period. Treatment emergent abnormalities of grade 2 or higher are those that were observed during the Treatment Period at scheduled visits and not reporting a grade 2 or higher abnormality during the Baseline Period. All treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher will be presented in a subject number listing.

Subject data listings of all laboratory data will also be presented. Within the listings TEMA values will be identified. Separate tables will also be provided to show the subject numbers of those who meet any of the TEMA and NCI CTC grade 2 or higher criteria.

Any additional lab data will be listed, including positive pregnancy test results listed by subject.

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

10.4.1 Vital signs

Observed values and changes from Baseline in vital sign parameters will be summarized using descriptive statistics for the scheduled visits. In addition, summary statistics for the observed value and change from Baseline will be presented for Last Visit, minimum, and maximum post-Baseline values obtained during the Treatment Period. Repeated or unscheduled assessments during the study will not be presented in by-visit summaries, but will be considered when determining the minimum, and maximum post-Baseline values during the Treatment Period.

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value, at each post-Baseline visit, for which systolic blood pressure, diastolic blood pressure, 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 time point. All TEMA results summarized will be presented in a subject number listing. The abnormal vital sign criteria are defined in Section 12.3.3.

A subject data listing of all vital signs data will be created, indicating any abnormal values.

10.4.2 Electrocardiograms

ECGs will be performed locally and no standardization techniques will be employed. The data will be analyzed as reported.

10.4.2.1 Derivation of corrected QT values

The Bazett corrected QT (QTcB) will be calculated as

$QT/\sqrt{RR}$, where RR = 60/heart rate.

The Fridericia corrected QT (QTcF) will be calculated as

$QT/\sqrt[3]{RR}$, where RR = 60/heart rate.

10.4.2.2 Analysis of ECG parameters

For quantitative ECG measurements (heart rate, PR interval, QRS interval, QT interval, RR Interval and corrected QT intervals using Bazett and Fridiricia correction methods), summary statistics of the actual values and change from Baseline will be summarized using descriptive statistics for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the TEMA ECG criteria age categories. Last visit is the value from the last post baseline visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values are listed.

The number and percentage of subjects who met each of the TEMA criteria specified in Section 12.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval, QRS interval, QT interval and corrected QT intervals by scheduled visit and Last Visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit values during the Treatment Period. Subject numbers for those with TEMA ECG values will be listed by abnormality criteria. TEMA results for a subject are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period.

Detailed information on the quantitative and qualitative ECG findings will be presented in subject data listings.

10.4.3 Physical examination

A listing of abnormal physical examination findings will be provided.

10.4.4 Safety Seizure Information

10.4.4.1 New Seizure Type

The number and percentage of subjects with seizure types present or absent in the Treatment Period vs whether the seizure type was present or absent in Combined Baseline will be tabulated. The number and percentage of subjects with seizure types present or absent in the Treatment Period vs whether the seizure type was present or absent in Seizure History (including Combined Baseline) will be tabulated.

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period with absence or myoclonic seizure type, respectively, indicated by the Seizure History Classification but not experienced in the Combined Baseline as recorded in the diary will be summarized.

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period but not experienced in the Combined Baseline or indicated in Seizure History Classification will also be summarized.

The number and percentage of subjects with new absence or myoclonic seizure types in the Treatment Period, with absence or myoclonic, respectively, indicated by the Seizure History Classification but not experienced in the Combined Baseline Period or subjects with ≥50% worsening in days with absence or myoclonic seizures, respectively, will be summarized.

10.4.4.2 Increase in days with absence seizures

Response to treatment regarding absence seizures will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.2. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with absence seizures per 28 days during the Treatment Period compared to the Prospective Baseline Period will be presented.

10.4.4.3 Increase in days with myoclonic seizures

Response to treatment regarding myoclonic seizures will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.2. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with myoclonic seizures per 28 days during the Treatment Period compared to the Prospective Baseline Period will be presented.

10.4.4.4 Increase in absence seizure frequency

Response to treatment regarding absence seizures will also be based on the percent change in the absence seizure frequency per 28 days, calculated as described in Section 8.3.1.9. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in absence seizure frequency per 28 days during the Treatment Period compared to the Prospective Baseline Period will be presented.

10.4.4.5 Increase in myoclonic seizure frequency

Response to treatment regarding myoclonic seizures will also be based on the percent change in the myoclonic seizure frequency per 28 days, calculated as described in Section 8.3.1.9. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in myoclonic seizure frequency per 28 days during the Treatment Period compared to the Prospective Baseline Period will be presented.

10.4.5 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 2 or who will enter puberty during the course of the study).

A listing of Tanner stage assessments will be provided.

10.4.6 Neurological examination

Summaries of shift from Baseline to Last Visit will be provided by major neurological category and treatment group based on categories normal, abnormal, not clinically significant, and abnormal, clinically significant. The major neurological categories collected on the CRF are General, Cranial Nerves, Reflexes, Motor System (including General, Muscle Strength and Muscle Tone), Coordination/Cerebellar Function and Sensation (including Upper and Lower Extremities). A listing of abnormal neurological examination findings will also be provided.

10.4.7 Assessment of suicidality

Suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). This 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 ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at the first visit 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 the "Since Last Visit" version should be used at subsequent visits. The C-SSRS is not validated for subjects <6 years of age and will not be used for this population.

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

10.4.8 Achenbach Child Behavior Checklist

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 4 years 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 all following visits, even if the subject passes the applicable age range during the study, and should be completed by the same parent/legal representative.

10.4.8.1 Derivation of Achenbach variables

The CBCL/1½-5 will be grouped according to syndrome scales in Table 2 and the CBCL/6-18 will be grouped according to empirically based syndrome scales in Table 3. The Achenbach CBCL has a 6 month recall. If a subject leaves the study early, and has been in the study for less than 6 months, this subject's data will not be included in the analysis and will be listed only.

Table 2: 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

Table 2: CBCL/1½-5

Syndrome scale	Questions
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

CBCL= Child Behavior Checklist

Table 3: 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

CBCL= Child Behavior Checklist

The Syndrome scale scores are calculated as the sum of the associated individual items scores. Each individual item score has the response options of:

0=not true (as far as known)

1=somewhat or sometimes true

2=very true or often true.

Missing data will not be replaced. Standardized T-scores are determined for each subject's raw syndrome and overall scores based on the subject's age and gender. Tables mapping each raw score to the appropriate T-score are provided in the CBCL Professional Manual and will be reproduced programmatically.

10.4.8.2 Analysis of Achenbach variables

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.

Subject data listings of the data for the Achenbach CBCL will be provided. The means of the calculated T-score will be plotted by visit.

10.4.9 BRIEF-P and BRIEF assessment

The BRIEF-P and BRIEF are validated tools that will be used for the evaluation of subjects ≥4 to <5 years of age, and ≥5 years of age, respectively. The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each subject, the same version (BRIEF-P or BRIEF) that is used at Visit 2 (Baseline) should be used at all following visits, even if the subject passes the applicable age range during the study. The BRIEF-P and BRIEF have a 6 month recall. If a subject leaves the study early, and has been in the study for less than 6 months, this subject's data will not be included in the analysis and will be listed only.

10.4.9.1 BRIEF-P scores

The BRIEF-P form comprises of 63 questions which can be answered Never (scored as 1 point), Sometimes (scored as 2 points), and 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 4 .

Table 4: BRIEF-P questionnaire scoring

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

Table 4: BRIEF-P questionnaire scoring

Scale/Index	Questions
GEC Score	**1-63**

GEC=Global Executive Composite

Standardized T-scores are determined from each subject's raw GEC, inhibitory self-control, flexibility, emergent metacognition, and component scores based on the subject's age and gender. 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 to10. 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 each visit, and Last Visit, by treatment group.

All BRIEF-P assessment data will be listed. The means of the BRIEF-P assessment data will be plotted by visit.

10.4.9.2 BRIEF scores

The BRIEF form comprises of 86 questions which can be answered as Never (scored as 1 point), Sometimes (scored as 2 points), and 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 5 .

Table 5: 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

Table 5: BRIEF questionnaire scoring

Scale/Index	Questions
BRI	**All from {Inhibit, Shift, and Emotional Control}**
Initiate	3, 10, 16, 47, 48, 61, 66, 71
Working Memory	2, 9, 17, 19, 24, 27, 32, 33, 37, 57
Plan/Organize	11, 15, 18, 22, 35, 36, 40, 46, 51, 53, 58
Organization of Materials	4, 29, 67, 68, 69, 72
Monitor	14, 21, 31, 34, 42, 52, 60, 63
MI	**All from {Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor}**
GEC Score	**1-72**

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

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 gender. 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 each visit, and Last Visit, by treatment group.

All BRIEF assessment data will be listed. The means of the BRIEF assessment data will be plotted by visit.

10.4.10 Vagus nerve stimulation

Vagus nerve stimulation (VNS) status is recorded only for subjects with an implanted VNS device.

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

10.4.11 Ketogenic diet

A listing of ketogenic diet findings will be provided.

11 REFERENCES

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12 APPENDICES

12.1 Appendix 1: QOLIE-31-P total and subscale score calculations

The following outlines the calculation of the subscale scores for the QOLIE‑31‑P. The rescaled responses are provided for each item. The subscale scores are calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. Note that the divisors shown assume that all items for each subscale have a response; the divisor will differ if there are missing responses. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Response Final Score

	Response							Final Score
Scale/Item Numbers	1	2	3	4	5	6	Subtotal	0-100 point scale
Seizure Worry								
30.	0	20	40	60	80	100	_____	
31.	0	33.3	66.7	100	—	—	_____	
32.	0	50	100		—	—	_____	
33.	0	33.3	66.7	100	—	—	_____	
34.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 5 = _____
Overall Quality of Life								
1.	Multiply each response by 10						_____	
36.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 2 = _____
Emotional Well-Being								
7.	0	20	40	60	80	100	_____	
8.	0	20	40	60	80	100	_____	
9.	100	80	60	40	20	0	_____	
10.	0	20	40	60	80	100	_____	
11.	100	80	60	40	20	0	_____	
						TOTAL :	_____	÷ 5 = _____

Energy/Fatigue

2.	100	80	60	40	20	0	_____
3.	100	80	60	40	20	0	_____
4.	0	20	40	60	80	100	_____
5.	0	20	40	60	80	100	_____

TOTAL : _____ ÷ 4 = _____

Cognitive Functioning

19.	0	20	40	60	80	100	_____
20.	0	33.3	66.7	100	—	—	_____
21.	0	20	40	60	80	100	_____
22.	0	20	40	60	80	100	_____
23.	0	20	40	60	80	100	_____
24.	100	75	50	25	0	—	_____

TOTAL : _____ ÷ 6 = _____

Medication Effects

28.	0	33.3	66.7	100	—	—	_____
26.	100	75	50	25	0	—	_____
27.	100	75	50	25	0	—	_____

TOTAL : _____ ÷ 3 = _____

Daily Activities/Social Functioning

13.	0	20	40	60	80	100	_____
14.	0	25	50	75	100	—	_____
15.	0	25	50	75	100	—	_____
16.	100	75	50	25	0	—	_____
17.	100	75	50	25	0	—	_____

TOTAL : _____ ÷ 5 = _____

Total score is calculated as a weighted sum of the subscale scores based on the weighting shown below. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

QOLIE-31-P Scale		Final Scale Score		Weight		Subtotal
Seizure worry	(a)	_____	×	0.08	=	_____
Overall quality of life	(b)	_____	×	0.14	=	_____
Emotional well-being	(c)	_____	×	0.15	=	_____
Energy/fatigue	(d)	_____	×	0.12	=	_____
Cognitive functioning	(e)	_____	×	0.27	=	_____
Medication effects	(f)	_____	×	0.03	=	_____
Daily activities/Social functioning	(g)	_____	×	0.21	=	_____
TOTAL SCORE : Sum subtotals (a) through (g)						_____

12.2 Appendix 2: Adverse Events

12.2.1 Other Significant AEs

Table 6: Other Significant AEs

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

MedDRA Preferred Term
Ventricular flutter
Ventricular tachyarrhythmia
Implantable defibrillator insertion
SUICIDALITY RELATED TERMS
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
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder
Decreased appetite
Diet refusal
Hypophagia
Food allergy

MedDRA Preferred Term
Abnormal behavior

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

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

Table 7: AEs for PDILI

MedDRA Preferred Term for PDILI
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Drug-induced liver injury
Hepatitis cholestatic
Hyperbilirubinaemia
Icterus index increased
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Mixed liver injury
Ocular icterus
Acute hepatic failure
Asterixis
Cholestatic liver injury
Coma hepatic
Cryptogenic cirrhosis

Drug-induced liver injury
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic failure
Hepatic infiltration eosinophilic
Hepatic necrosis
Hepatic steatosis
Hepatitis fulminant
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatotoxicity
Liver disorder
Liver injury
Mixed liver injury
Non-alcoholic steatohepatitis
Subacute hepatic failure
Allergic hepatitis
Chronic hepatitis
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent

Hepatitis fulminant
Hepatitis toxic
Non-alcoholic steatohepatitis
Blood bilirubin abnormal
Blood bilirubin increased
Hyperbilirubinaemia

12.3 Appendix 3: Markedly abnormal values

12.3.1 Hematology

Table 8: Hematology - Markedly Abnormal Values

Parameter	Age Range	UNIT (conventional)	Abnormality Criteria (conventional unit)	Unit (standard)	Abnormality Criteria (standard unit)
Hematocrit	2y - <17y	%	≤29 >47	%	≤29 >47
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
Hemoglobin	2y - <17y	g/dL	≤9.5 >16.0	g/L	≤95 >160
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
WBC/ Leukocytes	All	10^9/L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0
Lymphocytes Absolute	2y - <6y	10^9/L	<0.7 >6.9	G/L	<0.7 >6.9
	≥6y		<0.6 >5.0		<0.6 >5.0
Basophils	>1m	%	≥5.0	%	≥5.0
Basophils Absolute	>1m	10^9/L	≥0.4	G/L	≥0.4
Eosinophils	>1m	%	≥10	%	≥10
Eosinophils Absolute	>1m	10^9/L	≥1.0	G/L	≥1.0
Monocytes	>1m	%	≥20.0	%	≥20.0
Monocytes Absolute	>1m	10^9/L	≥2.0	G/L	≥2.0
Neutrophils Absolute	>1m	10^9/L	<1.5	G/L	<1.5
Platelets	>1m	10^9/L	≤100 ≥600	G/L	≤100 ≥600
RBC/ Erythrocytes	≥2y	10^{12}/L	<3.5	T/L	<3.5

Abbreviations: ANC = absolute neutrophil count; LLN = lower limit of normal; m = month; ULN = upper limit of normal; y = year.

A month is defined as 30 days; a year is defined as 365.25 days.

12.3.2 Chemistry

Table 9: Chemistry: Markedly Abnormal Values

PARAMETER	AGE RANGE	UNIT (conventional)	ABNORMALITY CRITERIA (conventional)	UNIT (standard)	ABNORMALITY CRITERIA (standard)
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 - <10y	U/L	≥834	U/L	≥834
	10y - <17y		≥1761		≥1761
	≥17y		≥3.0 x ULN		≥3.0 x ULN
GGT	1y - <13y	U/L	≥66	U/L	≥66
	13y - <17y		≥126		≥126
	≥17y		≥3.0 x ULN		≥3.0 x ULN
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	1y - <17y	g/dL	<4.3 >12.0	g/L	<43 >120
	≥17y		<4.3 >13.0		<43 >130
Albumin	≥1y - <17y	g/dL	<2.4 >8.4	g/L	<24 >84
	≥17y		<2.6		<26
BUN	1y - <17y	mg/dL	≥36	mmol/L	≥12.852
	≥17y		≥40		≥14.28
Urea	≥1y	mg/dL	>60	mmol/L	>10.02
Creatinine	1y - <10y	mg/dL	>1.2	umol/L	>106.8
	10y - <16y		>1.8		>159.12
	≥16y		≥2.0		≥176.8
Creatinine Clearance*	All	mL/min	<50	mL/s	<0.835

PARAMETER	AGE RANGE	UNIT (conventional)	ABNORMALITY CRITERIA (conventional)	UNIT (standard)	ABNORMALITY CRITERIA (standard)
Bicarbonate	>1m - <17y	mEq/L	<15 >38	mmol/L	<15 >38
	⩾17y		<18 >38		<18 >38
Calcium	1y - <17y	mg/dL	<7.4 >11.7	mmol/L	<1.85 >2.925
	⩾17y		⩽7.6 ⩾11.0		⩽1.9 ⩾2.75
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112
Phosphorous	1y - <17y	mg/dL	<1.8 >7.4	mmol/L	<0.5814 >2.3902
	⩾17y		⩽2.0 ⩾6.0		⩽0.646 ⩾1.938
Potassium	⩾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		<50 ⩾200		<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		>200		>5.18
HDL	>2y	mg/dL	<20	mmol/L	<0.518
Triglycerides	⩾1y	mg/dL	>300	mmol/L	>3.39
Uric Acid	1y - <13y	mg/dL	>6.5	umol/L	>386.62
	13y - <17y		>8.6		>511.528
	⩾17y		>9.5		>565.06
Thyroxine (T4)	⩾1y	ug/dL	⩽3.8 ⩾13.5	nmol/L	⩽48.9098 ⩾173.7585
Globulin	⩾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; L = liter; LLN = lower limit of normal; m = month; mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = year.

*Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine Cockroft equation (subjects >12);
Male: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine);
Female: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85.

12.3.3 Vital signs

Abnormality criteria to be applied in the assessment of vital signs parameter values are given below:

Table 10: Vital Signs - Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥120 and an increase from Baseline of ≥15 <60[a] >100[a]
Systolic Blood Pressure (mmHg)	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20 <90[a] >140[a] >160[a]
Diastolic Blood Pressure (mmHg)	3y - <12y	<50 >80
	12y - <17y	≤50 ≥105
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥105 and an increase from Baseline of ≥ 15 <50[a] >90[a] >100[a]
Body Weight	1m - <17y	<3% or >97% of the normal body weight growth curve ranges based on gender and the age of subject on date of weight assessment[a]
	≥17y	≥ 10% change from Baseline (an increase or a decrease)[b] ≥7% change from Baseline (an increase or a decrease)[a]

Abbreviations: y = year.

A month is defined as 30 days; a year is defined as 365.25 days.

[a] Type C Meeting Written Response Dated 4 Mar 2019 (Response to the Type C Meeting Request submitted on Dec 12, 2018 to IND 057939 Sequence No. 1268 cross-reference IND 068407 and IND 073809)

[b]source: http://www.cdc.gov/growthcharts/

12.3.4 ECGs

Abnormality criteria to be applied in the assessment of ECG parameter values are given below:

Table 11: ECGs - Abnormality Criteria

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	≥500
	≥12y	<450, 450-<480, 480-<500, ≥500 or <30, 30-<60, ≥60 increase from Baseline
QTc(F) (ms)	3y-<12y	>440, or >15% increase from Baseline
	≥12y- <17y	>440, or >15% increase from Baseline
	≥17y	<450, 450-<480, 480-<500, ≥500 or <30, 30-<60, ≥60 increase from Baseline >450, >480[a]
QTc(B) (ms)	3y-<12y	>450, or >15% increase from Baseline
	≥12y- <17y	>450, or >15% increase from Baseline
	≥17y	<450, 450-<480, 480-<500, ≥500 or <30, 30-<60, ≥60 increase from Baseline >450, >480[a]
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)	3y-<12y	>100, or ≥25% increase from Baseline
	≥12y - <17y	≥110, or ≥25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	3y-<12y	<60, >130
	≥12y	<50, >120

[a] Type C Meeting Written Response dated 4 Mar 2019 (Response to the Type C Meeting Request submitted on Dec 12, 2018 to IND 057939 Sequence No. 1268 cross-reference IND 068407 and IND 073809)

Abbreviations: bpm = beats per minute; m = month; ms = milliseconds; QTc = corrected QT interval; y = years.

A month is defined as 30 days; a year is defined as 365.25 days.

Note: 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.

12.4 Appendix 4: NCI CTC

Table 12: NCI CTC

Medical Term	Lab parameter	Grade 1	Grade 2	Grade 3	Grade 4
Blood/bone marrow					
Anemia	Hemoglobin	<LLN - 10.0 g/dL (C) <LLN - 6.2 mmol/L <LLN -100 g/L (S)	<10.0 - 8.0 g/dL (C) <6.2 - 4.9mmol/L <100 - 80g/L (S)	<8.0 g/dL (C) <4.9 mmol/L <80 g/L (S)	*
Neutrophil count decreased	Neutrophil count	<LLN - 1500/mm3 <LLN - 1.5 x10e9 /L (C) <LLN – 1.5G/L (S)	<1500 - 1000/mm3 <1.5 - 1.0 x10e9/L (C) <1.5 - 1.0G/L (S)	<1000 - 500/mm3 <1.0 - 0.5 x10e9/L (C) <1.0 - 0.5G/L (S)	<500/mm3 <0.5 x 10e9/L (C) <0.5G/L (S)
White blood cell decreased	White blood cell (WBC)	<LLN - 3000/mm3 <LLN - 3.0x10e9/L (C) <LLN - 3.0G/L (S)	<3000 - 2000/mm3 <3.0 - 2.0x10e9/L (C) <3.0 - 2.0G/L (S)	<2000 - 1000/mm3 <2.0 - 1.0x10e9/L (C) <2.0 - 1.0G/L (S)	<1000/mm3 <1.0 x 10e9/L (C) <1.0G/L (S)
Platelet count decreased	Platelet count	<LLN - 75,000/mm3 <LLN -75.0 x 10e9/L(C) <LLN -75.0G/L (S)	<75,000 - 50,000/mm3 <75.0 -50.0 x 10e9/L(C) <75.0 -50.0G/L (S)	<50,000 - 25,000/mm3 <50.0 -25.0 x 10e9/L(C) <50.0 -25.0G/L (S)	<25,000/mm3 <25.0 x 10e9/L(C) <25.0G/L (S)
Lymphocyte count decreased	Lymphocyte count	<LLN-800/mm3 <LLN-0.8x10e9/L (C) <LLN-0.8G/L (S)	<800 -500/mm3 <0.8 – 0.5x10e9/L (C) <0.8 – 0.5G /L (S)	<500 - 200/mm3 <0.5 – 0.2x10e9/L (C) <0.5 – 0.2G/L (S)	<200mm3 <0.2x10e9/L (C) <0.2G/L (S)
Metabolic/chemistry					
GGT increased	Gamma glutaryl transferase	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hypercalcemia	Calcium, corrected serum	>ULN - 11.5 mg/dL (C) >ULN - 2.9mmol/L (S)	>11.5 - 12.5 mg/dL (C) >2.9 - 3.1mmol/L (S)	>12.5 - 13.5 mg/dL (C) >3.1 - 3.4mmol/L (S)	>13.5 mg/dL (C) >3.4 mmol/L (S)
Hypocalcemia	Calcium, corrected serum	<LLN - 8.0 mg/dL (C) <LLN - 2.0mmol/L (S)	<8.0 - 7.0 mg/dL (C) <2.0 - 1.75 mmol/L (S)	<7.0 - 6.0 mg/dL (C) <1.75 - 1.5mmol/L (S)	<6.0 mg/dL (C) <1.5 mmol/L (S)
Hyperglycemia	Glucose, fasting	>ULN -160 mg/dL (C) >ULN - 8.9 mmol/L (S)	>160 -250 mg/dL (C) >8.9 - 13.9 mmol/L (S)	>250 - 500 mg/dL (C) >13.9 - 27.8mmol/L (S)	>500 mg/dL (C) >27.8 mmol/L (S)
Hypoglycemia	Glucose	<LLN - 55 mg/dL (C) <LLN - 3.0mmol/L (S)	<55 - 40 mg/dL (C) <3.0 - 2.2mmol/L (S)	<40 - 30 mg/dL (C) <2.2 - 1.7mmol/L (S)	<30 mg/dL (C) <1.7 mmol/L (S)
Hyperkalemia	Potassium	>ULN - 5.5 mmol/L (S)	>5.5 - 6.0 mmol/L (S)	>6.0 - 7.0 mmol/L (S)	>7.0 mmol/L (S)
Hypokalemia	Potassium	<LLN - 3.0 mmol/L (S)	*	<3.0 - 2.5 mmol/L (S)	<2.5 mmol/L (S)
Hypernatremia	Sodium	>ULN - 150 mmol/L (S)	>150 - 155 mmol/L (S)	>155 - 160 mmol/L (S)	>160 mmol/L (S)

Medical Term	Lab parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	Sodium	<LLN - 130 mmol/L (S)	*Not defined*	<130 - 120 mmol/L (S)	<120 mmol/L (S)
Hyper-triglyceridemia	Triglycerides	150 - 300 mg/dL (C) 1.71 - 3.42 mmol/L (S)	>300 - 500 mg/dL (C) >3.42 - 5.7 mmol/L (S)	>500 - 1000 mg/dL (C) >5.7 - 11.4 mmol/L (S)	>1000 mg/dL (C) >11.4 mmol/L (S)
Hyperuricemia	Uric acid	>ULN - 10 mg/dL (C) >ULN - 0.5948 mmol/L[a] >ULN – 594.8 umol/L (S)	*Not defined*	*	>10 mg/dL (C) >0.5948 mmol/L[a] >594.8 umol/L (S)
Hypoalbuminemia	Albumin	<LLN - 3 g/dL (C) <LLN - 30 g/L (S)	<3 - 2 g/dL (C) <30 - 20 g/L (S)	<2 g/dL (C) <20 g/L (S)	*
Hypo-phosphatemia	Phosphorus	<LLN - 2.5 mg/dL (C) <LLN - 0.8mmol/L (S)	<2.5 - 2.0 mg/dL (C) <0.8 - 0.6mmol/L (S)	<2.0 - 1.0 mg/dL (C) <0.6 - 0.3mmol/L (S)	<1.0 mg/dL (C) <0.3 mmol/L (S)
Alanine aminotransferase increased	Alanine amino-transferase (ALT)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate amino-transferase (AST)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	Bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Cholesterol high	Cholesterol, total	>ULN - 300 mg/dL (C) >ULN - 7.75mmol/L (S)	>300 - 400 mg/dL (C) >7.75-10.34 mmol/L (S)	>400 - 500 mg/dL (C) >10.34-12.92 mmol/L (S)	>500 mg/dL (C) >12.92 mmol/L (S)
Creatinine increased	Creatinine	>ULN - 1.5x ULN	>1.5 - 3.0x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN

Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal.
The cutoffs are according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
Published: May 28, 2009 (v4.03: June 14, 2010)
(C)=Conventional units, (S)=Standard units

12.5 Appendix 5: Registry Required Tables

The following is the list of tables required for Article 41 (EudraCT), clinicaltrials.gov and/or Article 46 (European Pediatric Regulation). These tables will be produced at the same time as the CSR required Tables.

Disposition and Discontinuation Reasons by Development

Discontinuation due to AEs

Demographics by Development

Baseline Characteristics by Development

ILAE Seizure Classification History by Development

Classification of Epileptic Syndrome by Development

AEDs and Benzodiazepines at Study Entry by Development

Summary of Time to Second PGTCS by Development

Proportion of Subjects with Seizure Freedom at Day 166 by Development

PGTCS Frequency Observed Results and Percent Changes from Combined Baseline by Development

Absence Seizure Frequency Observed Results and Percent Changes from Prospective Baseline by Development

Myoclonic Seizure Frequency Observed Results and Percent Changes from Prospective Baseline by Development

Responder Status for PGCTS by Development

Responder Status for Absence Seizure Frequency by Development

Responder Status for Myoclonic Seizure Frequency by Development

Seizure-free Status for PGTCS by Development

Days with Absence Seizures Observed Results and Percent Changes from Prospective Baseline by Development

Increase in Days with Absence Seizures During the Treatment Period Compared to Prospective Baseline by Development

Increase in Absence Seizure Frequency During the Treatment Period Compared to Prospective Baseline by Development

Responder Status and Seizure Worsening for Days with Absence Seizures by Development

Days with Myoclonic Seizures Observed Results and Percent Changes from Prospective Baseline by Development

Increase in Days with Myoclonic Seizures During the Treatment Period Compared to Prospective Baseline by Development

Increase in Myoclonic Seizure Frequency During the Treatment Period Compared to Prospective Baseline by Development

Responder Status and Seizure Worsening for Days with Myoclonic Seizures by Development

Incidence of Absence Seizure Emergence or Worsening by Development

Incidence of Myoclonic Seizure Emergence or Worsening by Development

Seizure-free Status for All Generalized Seizure Types by Development

Study Medication Duration by Development

Cumulative Study Medication Duration by Development

Study Medication Daily Dosing by Development

Incidence of TEAEs by Development – Overview

Incidence of TEAEs by Development

Incidence of Serious TEAEs by Development

Incidence of Non-serious TEAEs

Incidence of TEAEs by Relationship and Development

Incidence of TEAEs Leading to Discontinuation by Development

Incidence of Serious TEAEs by Relationship

Incidence of Non-serious TEAEs by Relationship

Incidence of Fatal TEAEs by Relationship

Incidence of Non-serious TEAEs Above Reporting Threshold of 5% of Subjects

Incidence of Non-serious TEAEs Above Reporting Threshold of 5% of Subjects by Relationship

12-Lead ECG Summary by Development

Treatment-Emergent Abnormal 12-Lead ECG Findings for Subjects by Development

12.6 Additional Subgroups to be programmed in ADSL

The following subgroup variable will also be programmed:

Subjects enrolled at Japanese study sites (Japanese, non-Japanese)

Subjects enrolled at Asian study sites (Asian, non-Asian) – Asian sites are those in Taiwan, South Korea, China and Japan

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

13.1 Amendment 1

13.1.1 Rationale for the amendment

The SAP was amended to reflect changes adopted in Protocol Amendment 5 v1.0 which affected the definition of the titration and maintenance periods and the rules for pooling strata with low numbers of events in the SAP. The compliance derivation was also updated to allow for subjects that take more than 2 tablets as they titrate to a higher dose.

13.1.2 Modification and changes

13.1.2.1 Specific changes

The information below was revised:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016

Has been changed to:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017

Section 3.2.1, the following text was changed from:

- Treatment Period: 24-week period following the 4-week Prospective Baseline. The Treatment Period is composed of the Titration Period and the Maintenance Period.
  - Titration Period: 6-week period following the 4-week Prospective Baseline. The Titration Period starts on the date of the Randomization Visit (Visit 2) and ends on the day before Visit 6 (or the date of the Early Termination (ET) visit in the situation where a subject discontinues prior to the last visit in the Titration Period).
  - Maintenance Period: 18-week period following the 6-week Titration Period. The Maintenance Period starts on the day of Visit 6 and continues until 1 of the following occurs (whichever occurs first):
    - Completion of ≥6 weeks of the Treatment Period, occurrence of ≥2 PGTC seizures and completion of the ET Visit
    - Completion of 18 weeks (Visit 10) of the Maintenance Period without occurrence of 2 PGTC seizures.

And revised as follows:

- Treatment Period: 24-week period following the 4-week Prospective Baseline. The Treatment Period is composed of the Titration Period and the Maintenance Period.
  - Titration Period: 6-week period following the 4-week Prospective Baseline. The Titration Period starts on the date of the Randomization Visit (Visit 2) and ends on the day before

Visit 5 (or the date of the Early Termination (ET) visit in the situation where a subject discontinues prior to the last visit in the Titration Period).

- Maintenance Period: 18-week period following the 6-week Titration Period. The Maintenance Period starts on the day of Visit 5 and continues until 1 of the following occurs (whichever occurs first):
  - Completion of ≥6 weeks of the Treatment Period, occurrence of ≥2 PGTC seizures and completion of the ET Visit
  - Completion of 18 weeks (Visit 10) of the Maintenance Period without occurrence of 2 PGTC seizures.

Section 7, the following bullet point was changed from:

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

And revised as follows:

- Compliance (%) = (Number of tablets dispensed – Number of tablets returned) / (Number of tablets prescribed per day x Number of days between x 100.

Section 8.1.2, the following text was changed from:

If no events (ie, no subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

- If no events occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
- If no events occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- If no events occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

And revised as follows:

If 5 events or less (ie, less than 6 subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

- If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.

- If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

Section 8.2.2.1, the following text was changed from:

If no events (ie, no subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

- If no events occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
- If no events occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- If no events occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

And revised as follows:

If 5 events or less (ie, less than 6 subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

- If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
- If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.

- Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

Section 8.2.2.3, the following text was changed from:

If no events (ie, no subjects who had a PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

- If no events occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
- If no events occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- If no events occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

And revised as follows:

If 5 events or less (ie, less than 6 subjects who had a PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

- If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
- If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
- Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

13.2 Amendment 2

13.2.1 Rationale for the amendment

The SAP was amended to include flexibility as an index for BRIEF-P.

13.2.2 Modification and changes

13.2.2.1 Specific changes

The information below was revised:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017

Has been changed to:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017
Amendment #2	14 Mar 2017

Section 10.4.9.1, the following text was changed from:

The BRIEF-P form comprises of 63 questions which can be answered Never (scored as 1 point), Sometimes (scored as 2 points), and Often (scored as 3 points).

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

The 2 subscale scores and 5 individual component scores that make up these subscale scores are outlined in Table 4 .

Table 4: BRIEF-P questionnaire scoring

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

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

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

And revised as follows:

The BRIEF-P form comprises of 63 questions which can be answered Never (scored as 1 point), Sometimes (scored as 2 points), and 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 4 .

Table 4: BRIEF-P questionnaire scoring

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

GEC=Global Executive Composite

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

13.3 Amendment 3

13.3.1 Rationale for the amendment

The SAP was amended to reflect changes adopted in Protocol Amendment 5 v4.0. The primary purpose of Protocol Amendment 5 v4.0 was to stop the subjects' study participation once 125 events are observed to avoid exposing subjects to placebo unnecessarily. This SAP amendment provides more detail in how PGTCS data will be analyzed for the primary and secondary efficacy endpoints. In general, all variables and all statistical analyses are more clarified.

13.3.2 Modification and changes

13.3.2.1 Specific changes

The information below was revised from:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017

Amendment #2	14 Mar 2017

has been revised to:

SAP/Amendment Number	**Date**
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017
Amendment #2	14 Mar 2017
Amendment #3	4 Jan 2019

The following abbreviations were revised from:

IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
IRT	Interactive response technology
LCM	lacosamide
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Metacognition Index
PCH	percent change
PedsQL	Pediatric Quality of Life Inventory
PGTC	primary generalized tonic-clonic

Has been revised to:

IGE	idiopathic generalized epilepsy
IIA	Absence seizures
IIB	Myoclonic seizures
IIC	Clonic seizures
IID	Tonic seizures
IIE	(primary generalized) tonic-clonic seizures
IIF	Atonic seizures
III	Unclassified seizures
ILAE	International League Against Epilepsy
IRT	Interactive response technology
KM	Kaplan-Meier
LCM	Lacosamide
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Metacognition Index

NCI CTC	National Cancer Institute Common Terminology Criteria for Adverse Events
PCH	percent change
PedsQL	Pediatric Quality of Life Inventory
PGTC	primary generalized tonic-clonic
PGTCS	Primary generalized tonic-clonic seizure

Section 2.2.1.2 Secondary efficacy variables were changed from:

The key secondary efficacy variable is:

- Seizure freedom for during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline)
- The percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline
- Time to the first PGTC seizure during the 24-week Treatment Period

And revised as follows:

The key secondary efficacy variable is:

- Seizure freedom for PGTCS during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variable is:

- Time to first seizure during the 24-week Treatment Period

Section 2.2.1.3 Other efficacy variables were changed from:

Other efficacy variables are:

- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Prospective Baseline
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the first 12 weeks of the Treatment Period compared to Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the Treatment Period compared to Combined Baseline
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- Change from Baseline to end of treatment or early termination (ET) in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject due to epilepsy
- Number of days with help from a caregiver due to epilepsy

And revised as follows:

Other efficacy variables are:

- The percent change in PGTCS frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Combined Baseline Period (combined 12-week Historical and 4-week Prospective Baseline Periods)
- The percent change in PGTCS frequency per 28 days during the first 12 weeks of the Treatment Period relative to the Combined Baseline Period

- The percent change in PGTCS frequency per 28 days during the Treatment Period relative to the Combined Baseline Period
- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline Period
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Prospective Baseline Period
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline Period
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline Period
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Prospective Baseline Period
- Seizure-free status (yes, no) for PGTCS for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTCS for the 24-week Treatment Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the Titration Period compared to Combined Baseline Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the first 12 weeks of the Treatment Period compared to Combined Baseline Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the Treatment Period compared to Combined Baseline Period
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age

- Change from Baseline to end of treatment or early termination (ET) in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject due to epilepsy
- Number of days with help from a caregiver due to epilepsy

Section 2.2.2 was revised from:

The safety variables are:

- Adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Changes in hematology, chemistry, endocrinology, and urinalysis parameters
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings
- Incidence of new seizure types during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

And revised as follows:

The safety variable is:

- Adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the investigator

Section 2.2.2.1 was revised from:

Other safety variables are:

- Behavioral assessment (Achenbach Child Behavior Checklist [CBCL]/1½-5 or CBCL/6-18)
- Cognitive function assessment (Behavior Rating Inventory of Executive Function®-Preschool Version [BRIEF-P] or Behavior Rating Inventory of Executive Function® [BRIEF])

And revised as follows:

Other safety variables are:

- Subject withdrawal due to AEs
- Incidence of new seizure types during the Treatment Period

- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Changes in hematology, chemistry, endocrinology, and urinalysis parameters
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings
- Behavioral assessment (Achenbach Child Behavior Checklist [CBCL]/1½-5 or CBCL/6-18)
- Cognitive function assessment (Behavior Rating Inventory of Executive Function®-Preschool Version [BRIEF-P] or Behavior Rating Inventory of Executive Function® [BRIEF]) for pediatric subjects only

Section 2.3.1, 2nd paragraph was revised from:

Approximately 200 subjects (100 per treatment arm) will be randomized to achieve a total of 125 events, where an event is defined as the occurrence of the second PGTC seizure.

Has been revised to:

Up to 250 subjects across 150 to 180 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study to see 125 events. An event is the occurrence of each subject's second PGTCS. The maximum duration of study medication administration is 28 weeks. The study will last a maximum of 36 weeks per subject.

Section 2.3.1, 5th paragraph, the following sentence was added:

Seizures reported on the Historical Seizure Count CRF with incomplete dates will be assumed to have occurred with the 12-week Historical Baseline Period when checking eligibility for the study and inclusion in baseline PGTCS frequency per 28 days.

Section 2.3.1, 2nd paragraph from end, newly states:

If the 125th event occurs while the subject is still participating in the study, the subject can:

- Complete the Visit 10 (Week 24) or ET Visit (if the next scheduled visit is not Visit 10) and choose to continue in EP0012 by completing a blinded transition followed by a Final Clinic Visit.
- Discontinue from the study by completing the Visit 10 (Week 24) or ET Visit (if the next scheduled visit is not Visit 10) and an up to 4-week blinded taper followed by an End of Taper visit.

Section 2.4, 2nd paragraph was revised from:

This is an event-driven study. The study will be closed to enrollment once 125 events have been observed. If 125 events are observed prior to 200 randomized subjects, then enrollment will stop

and fewer than 200 subjects will be randomized. However, if 125 events are not observed after 200 subjects are randomized, then the study will continue to enroll up to a maximum of 250 subjects randomized or 125 events, whichever occurs first.

Has been revised to:

This is an event-driven study. Enrollment in the study will continue up to 125 events occurring or a maximum of 250 subjects randomized, whichever comes first.

Section 3.1 was revised from:

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS® Version 9.4 or higher.

Descriptive statistics will be used to provide an overview of the primary, secondary, and other variable 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 the analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place except 100% which will be displayed to 0 decimal places. For continuous parameters, descriptive statistics will include number of subjects, mean, standard deviation, median, minimum, and maximum.

By-visit summaries will not include data from unscheduled clinic visits unless otherwise stated. Data provided at these visits will be included in subject data listings. Subject data listings will be provided and will present source data and key derived variables for statistical analyses.

Was revised to:

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS® Version 9.4 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be used to provide an overview of the primary, secondary, and other variable 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 the 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, mean, standard deviation, median, minimum, and maximum.

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

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

By-visit summaries will not include data from unscheduled clinic visits unless otherwise stated. Data provided at these visits will be included in subject data listings. A complete set of data listings containing all documented data and all calculated data (eg, change from Baseline) will be generated.

Section 3.2.1, Analysis Time Points, the following sentence was inserted:

First 12 weeks: this is defined as the Titration Period + the first 6 weeks of the Maintenance Period

Section 3.2.2, Seizure cluster, this section was moved to occur earlier in Section 3 and the text was revised from:

For PGTC seizures, if a seizure cluster is reported, it will be assigned to the most dominant ILAE seizure type and the frequency will be set to 2 times the number of clusters reported.

Was revised to:

If a seizure cluster is reported, it will be assigned to the International League Against Epilepsy (ILAE) seizure type reported and the frequency will be set to 2 times the number of clusters reported.

Section 3.2.3, Event, was added:

In the primary efficacy analysis, an event for analysis purposes is:

- The 2nd PGTCS

While keeping in mind the definition of seizure clusters in Section 3.2.2.

For the primary and secondary efficacy analyses, these endpoints will be assessed using the at most the first 166 days, which is the 24-week Treatment Period minus a protocol-allowed 2 day window. For all other efficacy parameters, all data reported during the Treatment Period will be used in the analysis.

The primary efficacy endpoint, time to event, is defined as the "stop date" - the date of first dose of study drug + 1 day where the "stop date" is the first of the following to occur:

- date of the event,
- date of the premature discontinuation,
- date of last dose of study medication in the Treatment Period,
- date of the completion of the Treatment Period,
- date of the 125th event,
- Day 166

The same algorithm applies for the other secondary endpoint, where time to event, is replaced by time to 1st PGTCS.

Section 3.2.4, Censoring, was revised from:

Subjects who complete the Treatment Period without having a second PGTC seizure during the Treatment Period will be censored. If the subject's Treatment Period participation is less than 24 weeks minus the visit window for Visit 10, they will be censored on the date of the last dose of study drug. If the subject's Treatment Period participation is greater than 24 weeks minus the visit window for Visit 10, they will be censored as of 24 weeks minus the visit window for Visit 10.

Subjects who have important protocol deviations for inappropriate use of AEDs and benzodiazepines will be censored. The important protocol deviations and rules for censoring due

to important protocol deviations will be determined and documented prior to the database lock and unblinding.

Has been changed to:

For the primary and secondary efficacy analyses, a Treatment Period of 166 days will be utilized. The censoring for the primary efficacy analysis will be as follows:

- Subjects who complete the Treatment Period without having an event during the Treatment Period will be censored as of Day 167.
- If the subject's Treatment Period participation is less than or equal to 166 days (premature discontinuation), their PGTCS information will be censored on the date after the last dose of study drug.
- If the subject's Treatment Period participation is greater than 166 days, their PGTCS information will be censored as of Day 167.
- For the subjects who are ongoing in the study when the 125th event occurs, their PGTCS information for the primary efficacy endpoint analysis will be censored as of the day after the 125th event, even if the subjects experience an event after the date of the 125th event but before 166 days of treatment is completed.
- Only 125 events will be included in the primary efficacy endpoint analyses. In case of ties on the same date in reporting the 125th event, the first event reported to IRT will be deemed the 125th event. Data after the 125th event will be censored.

Censoring for time to 1st PGTCS will be calculated in a similar manner, except using the date of the 1st PGTCS instead of the date of the event. For subjects who are ongoing in the study when the 125th event occurs, the time to 1st PGTCS information will be censored in the same manner as the time to event information (ie., censor all PGTCS information beyond the date of the 125th event).

Section 3.2.5, AEDs and Benzodiazepines, the 1st paragraph has been revised from:

Antiepileptic drugs and benzodiazepines (medications used for rescue) will be collected on the concomitant and prior medication case report form (CRF) for AEDs. At study entry, a subject should be taking 1 to 2 non-benzodiazepines or 1 to 3 AEDs where only 1 of the AEDs is identified as a benzodiazepine. This dosing regimen must be stable for at least 28 days prior to Visit 1. The subject must maintain this AED dosing regimen throughout the Prospective Baseline and the Treatment Period.

Has been changed to:

AEDs and benzodiazepines (medications used for rescue) will be collected on the concomitant and prior medication case report form (CRF) for AEDs. At study entry, a subject should be taking a stable dose of 1 to 2 non-benzodiazepines marketed AEDs or 2 to 3 AEDs (with only 1 of the AEDs is identified as a benzodiazepine). This dosing regimen must be stable for at least 28 days prior to Visit 1. The subject must maintain this AED dosing regimen throughout the Prospective Baseline and the Treatment Period with or without additional concurrent stable VNS. Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with

constant settings for at least 28 days prior to Visit 1 and must remain unchanged during the Treatment Period.

Section 3.2.5.1, Prohibited concomitant treatments, has been added:

The following medications/therapies are prohibited during the Treatment Period:

- Clozapine
- Any MAO inhibitors
- Barbiturates (except as antiepileptic medications)
- Unstable dosing of non-benzodiazepine anxiolytics or once-daily hypnotics
- Herbal medicines for epilepsy

The study physician will review the concomitant medications and flag prohibited medications.

Section 3.2.8, Month, has been added:

A month is defined as 28 days.

Section 3.3, Definition of baseline values, the 2nd paragraph had been revised from:

Baseline values for seizure data will be based on data collected during the Combined Baseline Period, excluding data collected on the day of Visit 2.

Has been revised to:

For PGTCS efficacy analyses, the data used for Baseline calculations come from the Combined Baseline Period. For absence and myoclonic seizure analyses, the data used for Baseline calculations come from the Prospective Baseline Period only.

Section 3.9, Changes to protocol-defined analyses, has been revised from:

There are no changes to analyses specified in the protocol.

Has been revised to:

For the key secondary efficacy variable, the Protocol Section 4.1.2 says that seizure freedom for PGTCS during the 24-week Treatment Period, will be estimated using Kaplan-Meier analysis. The analysis of the key secondary endpoint has been clarified to assess the seizure-free rate using an extended Mantel-Haenszel technique which combines Kaplan-Meier estimates within each stratum. The extended Mantel-Haenszel technique is a randomization-based nonparametric method that provides a more robust method to assess seizure freedom.

Section 4.2.1, Missing seizure diary days, 2nd paragraph has been revised from:

For the purpose of the derivation of the primary endpoint of time to second PGTC seizure and for PGTC seizure-free status, if there are seizure counts reported as “not done” on a specific day, then the seizure count will be assumed to be zero on that date.

Has been changed to:

For the purpose of the derivation of the primary efficacy endpoint, secondary efficacy endpoints and for PGTC seizure-free status, if there are PGTCS counts reported as “not done” on a specific day, then the PGTCS count will be assumed to be zero on that date.

Section 4.2.2, Incomplete dates for first epilepsy diagnosis, the following final imputation note was added:

- Missing the day, month and year:

No imputation will be done.

Section 4.4, Multicenter studies, was revised from:

Due to the small number of subjects per site, pooling the sites for statistical analysis will be necessary. All sites will be pooled together for analysis.

has been changed to:

Due to the small number of subjects per site, all sites will be pooled together for analysis. There will be no planned analyses for multi-center effects.

Section 4.8, Examination of subgroups, was revised from:

Descriptive statistics by all subgroups for the primary efficacy variable will be presented for the FAS. Disposition will be presented by age subgroup for the SS and FAS. Exposure will be presented by age and region subgroups for the SS. Overall TEAE incidence will be presented by age subgroup for the SS. Selected disposition and safety analyses will be presented by age at enrollment for the purpose of addressing requirements set in Article 46 of the European Pediatric Regulation (see Section 12.5 for further details).

The subgroups to be examined include:

- Age at enrollment (≥ 4 to <12 years of age, ≥12 to <18 years of age, 18 to <65, ≥65)
- Racial group (white, non-white)
- Gender (male, female)
- Region
  - North America: United States
  - Latin America: Brazil, Mexico
  - Western Europe: Belgium, France, Germany, Italy, Portugal, Spain
  - Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Turkey
  - Asia/Pacific/Other: Australia, Israel, Japan, South Korea, Taiwan
- Baseline PGTC seizure frequency (≤2 per 28 days and >2 per 28 days in the Combined Baseline Period)
- Concomitant AEDs at study entry, ie the total number of AEDs and benzodiazepines the subject is taking when enrolled into the study (1, 2, 3).

Separate age sub-groupings are used for the purpose of summarizing the following scales:

- PedsQL (4 years, ≥5 to ≤7 years, ≥8 to ≤12 years, and ≥13 to ≤18 years)
- Achenbach CBCL (4 to 5 years, 6 to 18 years)

- BRIEF-P/BRIEF (4 to <5 years, ≥5 years).

Has been changed to:

Descriptive statistics by all subgroups for the primary efficacy variable will be presented for the FAS. Disposition will be presented by age subgroup for the SS and FAS. Exposure will be presented by age and region subgroups for the SS. Overall TEAE incidence will be presented by age subgroup for the SS. Selected disposition and safety analyses will be presented by Development for the purpose of addressing requirements set in Article 46 of the European Pediatric Regulation (see Section 12.5 for further details).

The subgroups to be examined include:

- Age at enrollment (≥ 4 to <12 years of age, ≥12 to <18 years of age, 18 to <65, ≥65)
- Development (Pediatric [≥4 to < 18 years old], Adult [≥18 years old])
- Racial group (white, non-white)
- Gender (male, female)
- Region
  - North America: United States, Puerto Rico
  - Latin America: Brazil, Mexico
  - Western/Central Europe: Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain
  - Eastern Europe: Bulgaria, Romania, Russia, Turkey
  - Asia/Pacific/Other: Australia, China, Israel, Japan, South Korea, Taiwan
- Baseline PGTCS frequency (≤2 per 28 days and >2 per 28 days in the Combined Baseline Period)
- Concomitant AEDs at study entry, ie the total number of AEDs and benzodiazepines the subject is taking when enrolled into the study (1, 2, 3).

Separate age sub-groupings are used for the purpose of summarizing the following scales:

- PedsQL (4 years, ≥5 to ≤7 years, ≥8 to ≤12 years, and ≥13 to ≤18 years)
- Achenbach CBCL (4 to 5 years, 6 to 18 years)
- BRIEF-P/BRIEF (4 to <5 years, ≥5 years).

Section 4.9, Stratum Pooling has been moved from a later section and the algorithm modified from saying:

The analysis will use the stratification factors from IRT. If 5 events or less (ie, less than 6 subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

1. If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures

per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.

2. If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
3. If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
4. Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

Has been revised to:

The stratification factors for this study are Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analyses will use the stratification factors from IRT.

To determine if strata pooling should occur for time to event (2nd PGTCS) analysis:

For the subjects with Baseline PGTCS frequency ≤2 per 28 days, the events for each of the 3 age at informed consent categories will be summed.

- If 2 of the age at informed consent categories combined have < 3 total events, then all age categories are combined for the analysis.
- If ≥4 to <12 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥12 and <18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the strata with the 2nd smallest number of events.

For the subjects with Baseline PGTCS frequency >2 per 28 days, repeat the same exercise to determine stratum pooling.

Time to 1st PGTCS analyses:

The prior algorithm for stratum pooling will be used to determine stratum pooling, except that "events" will now be in reference to subjects having only 1 PGTCS.

Seizure freedom analyses:

The prior algorithm for stratum pooling will be used to determine stratum pooling, except that "events" will now be in reference to subjects having 0 PGTCS.

Section 5.1, Subject disposition, the 3rd paragraph was modified from:

The overall number and percentage of subjects who completed and discontinued from the study will be presented for the SS, FAS and PPS including number and percentages for each reason for

discontinuation. The completion of the study is defined as meeting any of the predetermined exit criteria or experiencing <2 PGTC seizures within the 24-week treatment period. Discontinuation is defined as the completion of the ET Visit. This summary will be repeated for specific subgroups as detailed in Section 4.8 for the SS and FAS. The study termination information will be presented in the subject data listings.

Has been changed to:

The overall number and percentage of subjects who completed and discontinued from the study will be presented for the SS, FAS, and PPS including number and percentages for each reason for discontinuation. The completion of the study is defined as meeting any of the predetermined exit criteria (including when the 125th event has occurred) or experiencing <2 PGTCS within the 24-week treatment period. Discontinuation is defined as the completion of the ET Visit in all other cases. This summary will be repeated for specific subgroups as detailed in Section 4.8 for the SS and FAS. The study termination information will be presented in the subject data listings.

Section 6.2.2, Analysis of baseline characteristics, the 2nd paragraph has been changed from:

The following Baseline characteristics will also be presented:

- Time since first diagnosis at date of consent
- Age at diagnosis of the disease
- International League Against Epilepsy (ILAE) Seizure classification history
- Classification of epileptic syndrome
- Etiology of epilepsy

Has been changed to:

The following Baseline characteristics will also be presented:

- Time since first diagnosis at date of consent
- Age at diagnosis of epilepsy
- Number of lifetime AEDs and Benzodiazepines (0, 1-3, 4-6, ≥7)
- Concomitant benzodiazepine use at study entry (yes, no)
- ILAE (1989) Seizure classification history
- Classification of epileptic syndrome
- Etiology of epilepsy

Section 7, Measurements of Treatment Compliance, the following text was removed:

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 x Number of days between x 100.

Rates of compliance will be calculated and summarized by category: <75%, 75-125%, >125%.

Section 8, Efficacy Analyses, were revised from:

All efficacy analyses will be performed using the FAS population.

For all efficacy analyses, only data up to and including the day of the second PGTC seizure, the Visit 10 date or the last maintenance dose date, whichever is earlier, will be included. All seizure diary data will be listed including data not included in the efficacy analyses.

Testing for the primary endpoint will be done at the 5% level (2-sided). Provided that the primary endpoint is statistically significant, a gatekeeping strategy will be used to test the key secondary efficacy variable. No additional adjustments for multiplicity are required as all additional inferences will be hypothesis-generating only.

Has been revised to:

Most efficacy analyses will be performed using the FAS population; in other cases, the population will be stated.

For primary efficacy endpoint analyses, only data up to and including the day of the event, the Visit 10 date, last Treatment Period dose date, Day 166 or the date of the 125th event, whichever is earlier, will be included. For the secondary efficacy endpoint analyses, only data up to and including the day of the first PGTCS, the Visit 10 date, the last Treatment Period dose date, Day 166 or the date of the 125th event, whichever is earlier, will be included. For all other exploratory efficacy variables, all appropriate seizure data during the Treatment Period, will be included. All seizure diary data will be listed including data not included in efficacy analyses.

Testing for the primary efficacy endpoint will be done at the 5% level (2-sided). Provided that the primary efficacy endpoint is statistically significant, a gatekeeping strategy will be used to test the key secondary efficacy variable, seizure freedom. No additional adjustments for multiplicity are required as all additional inferences will be hypothesis-generating only.

Section 8.1.1, Derivations of primary efficacy variable, has been revised from:

For PGTC seizures, the number of days until the second seizure will be derived using the date of the second PGTC seizure – date of first dose of study medication +1. For subjects who prematurely discontinue or complete the 24-week Treatment Period prior to having a second PGTC seizure, time to censor will be calculated as the date of censoring - date of first dose of study medication + 1. Only data up to Week 24 will be included. Censoring of subjects for this analysis will be as described in Section 3.2.2.If a day is marked in the CRF as “not done”, it will be assumed that no seizures occurred on that day.

Has been changed to:

For the primary efficacy variable, an event and how time to event is calculated is described in Section 3.2.3, keeping in mind Section 3.2.2. Censoring of subjects for this analysis will be as described in Section 3.2.4 . If a day is marked in the CRF as “not done”, it will be assumed that no seizures occurred on that day.

Section 8.1.2, Primary analysis of the primary efficacy variable, has been modified from:

The primary efficacy variable, time to second PGTC seizure during the 24-week Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT. If 5 events or less (ie, less than 6 subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

5. If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
6. If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
7. If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
8. Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

The stratified HR will be calculated using the placebo arm as the reference group.

Additionally, a KM plot for time to second PGTC seizure as well as the KM estimate for the median time to second PGTC seizure will be provided. If the median time is not estimable, then the 25th percentile will be provided.

Has been changed to:

The primary efficacy variable, time to event during the 166-day Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT and pooled as described in Section 4.9.

The hypothesis for the assessment of primary efficacy variable (time to event) is as follows:

$$H_0: \beta=0$$

Versus

$$H_1: \beta\neq0$$

where β is the coefficient of an independent variable representing the treatment effect in the model. The hazard function is represented by

$$h(t,X) = h_0(t)\exp(\sum_{j=1}^{p} \beta_j X_j$$

where x_j is the collection of independent variables and $h_0(t)$ is the baseline hazard at time t. For the null hypothesis, the testing will be 2-sided with an α=0.05; the p-value will be presented. The assumptions of proportional hazards will also be checked.

The stratified hazard ratio (HR) will be calculated using the placebo arm as the reference group. The SE and 95% CI for the HR will also be reported.

Additionally, a Kaplan-Meier (KM) plot for time to event as well as the KM estimate for the median time to event and 95% CI will be provided. If the median time is not estimable, then the 25th percentile and 95% CI will be provided. The number of events will be reported by treatment group for the Titration Period, first 12 Weeks, and Treatment Period as well as the % of subjects who were censored in the analysis.

Section 8.1.3, Secondary analyses of the primary efficacy variable, has been changed from:

The summary of time to the second PGTC seizure during the 24-week Treatment Period will be presented by subgroup for the FAS. A KM plot for time to second PGTC seizure by selected subgroups will also be provided.

Has been changed to:

The summary of time to the event during the 166-day Treatment Period will be presented by all subgroup for the FAS. A KM plot for time to second PGTCS by all subgroups will also be provided.

Section 8.1.4, Supportive and sensitivity analyses of the primary efficacy variable, has been changed from:

The following additional sensitivity analyses on the primary efficacy endpoint will be conducted in order to assess the effect of dropouts, important protocol deviations, and operational bias on the primary endpoint:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy, consent withdrawn, or lost to follow-up will be analyzed as treatment failures (ie, events at the time of discontinuation).
- Repeat the primary analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy or AEs only will be analyzed as treatment failures.
- Repeat the primary analysis using the FAS, comparing the event rates prior to vs after each interim analysis to examine possible operational bias due to unblinding.

Has been changed to:

The following additional sensitivity analyses on the primary efficacy endpoint will be conducted in order to assess the effect of dropouts, important protocol deviations, and operational bias on the primary endpoint:

- Repeat the primary efficacy analysis using the PPS.

- Repeat the primary efficacy analysis using all PGTCS data (ie, all reported events) through each subject's first 166 days of treatment, on the FAS.
- Repeat the primary efficacy analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy, consent withdrawn, or lost to follow-up will be analyzed as treatment failures (ie, events at the time of discontinuation).
- Repeat the primary efficacy analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy or AEs only will be analyzed as treatment failures.
- Repeat the primary efficacy analysis using the FAS, comparing the event rates prior to vs after each interim analysis to examine possible operational bias due to unblinding.

Section 8.2.1.1, Seizure freedom for PGTCS for the 166-day Treatment Period, has been modified from:

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

A subject will have seizure freedom (seizure free status=yes) for the 24-week Treatment Period if the subject completed the Treatment Period and reported zero seizures or "not done" for all days during the Treatment Period.

Has been changed to:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary and PGTCS were assessed. Days in the seizure diary which are marked as "not done" on the CRF will be counted as seizure-free days from PGTCS.

A subject will have seizure freedom from PGTCS for the 166-day Treatment Period if the subject completed the Treatment Period and reported zero PGTCS or "not done" for all days during the 166-day Treatment Period. Ongoing subjects who are seizure-free from PGTCS on the date of the 125th event do not have seizure-freedom from PGTCS unless they are seizure-free from PGTCS for 166 days.

Section 8.2.1.2, Time to 1st PGTCS during the 166-day Treatment Period, has been changed from:

For PGTC seizures, the number of days until the first seizure will be derived using the date of the first PGTC seizure – date of first dose of study medication +1. For subjects who prematurely discontinue or complete the 24-week Treatment Period prior to having a PGTC seizure, time to censor will be calculated as the date of censoring - date of first dose of study medication + 1. Only data up to Week 24 will be included. Censoring of subjects for this analysis will be as described in Section 3.2.2.

If a day is marked in the CRF as "not done", it will be assumed that no seizures occurred on that seizure diary day.

Has been changed to:

For PGTCS, how the time to first PGTCS is calculated is described in Section 3.2.3. Censoring of subjects for this analysis will be as described in Section 3.2.4 .

If a day is marked in the CRF as "not done", it will be assumed that no seizures occurred on that seizure diary day.

Section 8.2.2 has been updated to:

Analyses of secondary efficacy variables will be performed for the FAS.

Section 8.2.2.1: Seizure freedom for the 166-day Treatment Period, has been modified from:

Analysis of the key secondary efficacy variable, seizure freedom for PGTC seizures for the 24-week Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT. If 5 events or less (ie, less than 6 subjects who had a second PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

9. If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
10. If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
11. If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
12. Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

The percentage of seizure-free subjects at 24 weeks will be estimated from the KM estimates of time to first seizure using 2-sided 95% confidence intervals. A stratified estimate of the seizure freedom rate in each treatment arm will be derived using KM methods to estimate the seizure freedom rate for each stratum and then combining the rates using a Cochran-Mantel-Haenszel-like approach. The stratified HR will be calculated using the placebo arm as the reference group.

If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

Has been modified to:

Analysis of the key secondary efficacy variable, seizure freedom for PGTCS for the 166-day Treatment Period, will be evaluated using an extended Mantel-Haenszel testing procedure which takes into account that the subjects were initially stratified for the subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at

informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT and pooled as described in Section 4.9.

The hypothesis for the assessment of the key secondary efficacy (PGTC seizure-freedom) is as follows:

$$H_0: S(t=166)_{LCM} = S(t=166)_{PBO}$$

Versus

$$H_1: S(t=166)_{LCM} \neq S(t=166)_{PBO}$$

Where $S(t=166)$ is the cumulative rate of subjects remaining seizure-free from PGTCS for 166 days.

Estimation of treatment difference:

KM methods will be used to estimate the proportion of subjects remaining seizure-free from PGTCS at Day 166. The estimate for the difference in Day 166 seizure-freedom from PGTCS will be adjusted for subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The estimate for the stratified difference in proportion of subjects who are seizure-free from PGTCS on LCM vs PBO and a corresponding 95% two-sided confidence interval ($CI_{LCM-PBO}$) will be produced using mantel Haenszel methods (LaVange et al, 2005). The statistical methodology is expressed as follows:

$$d=\sum_{h=1}^{6} w_h(S_{h1}-S_{h2})$$

Where S_{hi}=KM estimate of 166-day seizure freedom from PGTCS for treatment i (1=LCM and 2=PBO) in stratum h (1= ≤2 per 28 days Baseline PGTCS frequency and ≥ 4 to <12 years of age, 2= ≤2 per 28 days Baseline PGTCS frequency and ≥12 to <18 years of age, 3= =≤2 per 28 days Baseline PGTCS frequency and ≥18 years of age, 4= >2 per 28 days Baseline PGTCS frequency and ≥ 4 to <12 years of age, 5= >2 per 28 days Baseline PGTCS frequency and ≥12 to <18 years of age and 6= >2 per 28 days Baseline PGTCS frequency and ≥18 years of age and $w_h=\{(n_{h1}*n_{h2})/(n_{h1}+n_{h2})\}/\sum_{h=1}^{6}\{(n_{h1}*n_{h2})/(n_{h1}+n_{h2})\}$

where n_{hi} is the number of subjects in I treatment group and stratum h. The variance of d is calculated as $Var(d)=\sum_{h=1}^{6} w_h^2\{\mathrm{Var}(S_{h1})+\mathrm{Var}(S_{h2})\}$ where $Var(S_{h1})$ and $Var(S_{h2})$ are the Greenwood estimates of variance for S_{h1} and S_{h2}.

The stratified proportion of subjects remaining seizure free from PGTCS for at least 166 days in each treatment group and the associated variance are derived as follows using Mantel Haneszel methods:

The KM estimate for the LCM 166-day seizure-freedom from PGTCS rate is calculated as $S_1=\sum_{h=1}^{6} w_h S_{h1}$

The KM estimate for the PBO 166-day seizure-freedom from PGTCS rate is calculated as $S_2=\sum_{h=1}^{6} w_h S_{h2}$

The variance is S1 is calculated as $Var(S_1)=\sum_{h=1}^{6} w_h^6 Var(S_{h1})$

The variance of S2 is calculated as $Var(S_2)=\sum_{h=1}^{6} w_h^6 Var(S_{h2})$

In order to assess superiority, 2-sided testing with α=0.05 will be used. The superiority test statistic, $Q=d^2/Var(d)$ will be assessed by a chi-square distribution with 1 degree of freedom. This statistic is referred to as the "row mean score statistic" when using Proc Freq.

The number and percentage of subjects who experience a PGTCS or censoring and the KM seizure-free rate from PGTCS (and 2-sided 95% CI) by Day 166 will be presented by treatment group for each stratum and overall. The stratified seizure-freedom rate from PGTCS (and 2-sided 95% CI) at Day 166 for each treatment group and the difference between treatment groups will be presented. A Kaplan-Meier plot will be presented by treatment group for each stratum and overall.

For the gatekeeping strategy, if the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

Section 9.2.2.2, Analysis of Percent Change in PGTC seizure frequency from Combined Baseline has been removed from the SAP.

The percent change in log-transformed PGTC seizure frequency during the first 6 weeks of the Treatment Period will be analyzed using analysis of covariance, controlling for Baseline seizure frequency.

The percent change in log-transformed PGTC seizure frequency during the Treatment Period will be analyzed analysis of covariance, controlling for Baseline seizure frequency.

All PGTC seizure frequency per 28 days data will be listed.

Section 8.2.2.2, Time to first PGTCS during the 166-day Treatment Period, has been changed from:

Time to the first PGTC seizure during the 24-week Treatment Period will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT. If 5 events or less (ie, less than 6 subjects who had a PGTC seizure) occur in a stratum, then data will be pooled by Baseline PGTC seizure frequency for analysis as follows:

13. If 5 events or less occur in the group of subjects who are ≥12 and <18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with either the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days or the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, whichever has the smallest number of events.
14. If 5 events or less occur in the group of subjects who are ≥4 to <12 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.

15. If 5 events or less occur in the group of subjects who are ≥18 years of age with ≤2 Baseline PGTC seizures per 28 days, then this group will be combined for analysis with the group of subjects who are ≥12 to <18 years of age with ≤2 Baseline PGTC seizures per 28 days.
16. Similarly, rules 1 to 3 apply to those age groups within subjects with > 2 Baseline PGTC seizures per 28 days.

The stratified HR will be calculated using the placebo arm as the reference group.

Additionally, a KM plot for time to first PGTC seizure as well as the KM estimate for the median time to first PGTC seizure will be provided. If the median time is not estimable, then the 25th percentile will be provided.

Has been changed to:

Time to the first PGTCS during the 24-week Treatment Period will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). The analysis will use the stratification factors from IRT and pooled as described in Section 4.9.

The hypothesis for the assessment of the time to first PGTCS is as follows:

$$H_0: \beta=0$$

Versus

$$H_1: \beta\neq0$$

where β is the coefficient of an independent variable representing the treatment effect in the model. The hazard function is represented by

$$h(t,X) = h_0(t)\exp(\sum_{j=1}^{p} \beta_j X_j$$

where x_j is the collection of independent variables and $h_0(t)$ is the baseline hazard at time t. For the null hypothesis, the testing will be 2-sided with an α=0.05. The assumptions of proportional hazards will also be checked.

The stratified HR will be calculated using the placebo arm as the reference group. The SE and 95% CI for the HR will also be reported.

Additionally, a KM plot for time to 1st PGTCS as well as the KM estimate for the median time to 1st PGTCS and 95% CI will be provided. If the median time is not estimable, then the 25th percentile and 95% CI will be provided. The number of 1st PGTCS will be reported by treatment group for the Titration Period, first 12 Weeks, and Treatment Period as well as the % of subjects who were censored.

Section 8.3, the following sentence has been added:

All seizure data recorded during the treatment period will be summarized and listed for the seizure related other efficacy variables. Analyses of seizure-related other efficacy variables will be performed for the FAS.

Section 8.3.1.2 Days with seizures per 28 days, the following sentence was added to the 2nd to last paragraph:

PCH will be calculated for the 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

Section 8.3.1.3, Seizure-free status, was modified from:

Refer to Section 8.2.1.1 for PGTC seizure-free status.

A subject will have seizure freedom (seizure free status=yes) for all generalized seizure types for the applicable Treatment Period if the subject completed the Treatment Period and reported zero generalized seizures for all days during the Treatment Period when the number of seizures was available, and had <10% of days during the Treatment Period with seizure data reported as "not done".

Has been changed to:

A subject will have seizure-free status for PGTCS=yes for the Treatment Period if the subject completed the Treatment Period (with a minimum 166 days) and reported zero PGTCS or "not done" for all days during the Treatment Period. If the subject is exited from the study due to the 125th event occurring reporting zero PGTCS or "not done" for all days and duration of the Treatment Period is < 166 days, then the subject has not achieved seizure-free status for PGTCS.

A subject will have seizure free status=yes for all generalized seizure types for the applicable Treatment Period if the subject completed the Treatment Period and reported zero generalized seizures for all days during the Treatment Period when the number of generalized seizures was available, and had <10% of days during the Treatment Period with seizure data reported as "not done".

Seizure-free statuses will be calculated for 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

Section 8.3.1.4, Responder status – reduction in PGTCS frequency, has been changed from:

Response to treatment regarding PGTC seizure frequency will be based on the percent change in seizure frequency, calculated as described in Section 8.3.1.1. A responder is defined as a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the period of interest (first 12 weeks of the Treatment Period or the 24-week Treatment Period).

Has been changed to:

Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.3.1.1 . A 50% responder is defined as a subject experiencing ≥50% reduction in PGTCS frequency per 28 days from the Combined Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in PGTCS frequency per 28 days from Combined Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

Section 8.3.1.5 PGTCS worsening, is new:

Seizure worsening is defined as a subject experiencing ≥50% increase in PGTCS frequency per 28 days from Combined Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

Section 8.3.1.6 Responder status – reduction in days with absence seizures, is new:

Response to treatment for absence seizures per 28 days will be based on the percent change in days with absence seizures, calculated as described in Section 8.3.1.2. A 50% responder is defined as a subject experiencing ≥50% reduction in days with absence seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in days with absence seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

Section 8.3.1.7 Responder status – reduction in days with myoclonic seizures, is new:

Response to treatment for myoclonic seizures per 28 days will be based on the percent change in days with myoclonic seizures, calculated as described in Section 8.3.1.2. A 50% responder is defined as a subject experiencing ≥50% reduction in days with myoclonic seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in days with myoclonic seizures per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

Section 8.3.2.1, Percent Change in PGTCS frequency per 28 days from Combined Baseline, is new:

Descriptive statistics will be provided on the percent change in PGTCS frequency for the first 6 weeks of (entire Titration Period), first 12 weeks of, and the entire Treatment Period.

All PGTCS frequency per 28 days data will be listed.

Section 8.3.2.2 Reduction in days with seizures per 28 days was changed from:

The following data will be summarized with descriptive statistics only:

- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to the Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to the Prospective Baseline

All seizure days data for absence and myoclonic seizures will be listed.

Has been changed to:

The following data will be summarized with descriptive statistics only:

- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 12 weeks of the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 12 weeks of the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

All seizure days data for absence and myoclonic seizures will be listed.

Section 8.3.2.3, Seizure-free status, was modified from:

The following seizure-free status (yes/no) summaries will be provided:

- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period

Has been changed to:

The following seizure-free status (yes/no) summaries will be provided:

- Seizure-free status (yes, no) for PGTCS for the first 6 weeks of the Treatment Period (Titration Period)
- Seizure-free status (yes, no) for PGTCS for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTCS for the 24-week Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the first 6 weeks of the Treatment Period (Titration Period)
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period

Section 8.3.2.4, Responder status – reduction in PGTCS frequency

The number and percentage of responders will be summarized with descriptive statistics only for the following periods of interest:

- PGTC seizures during the first 12 weeks of the Treatment Period
- PGTC seizures during the 24-week Treatment Period

A histogram of ≥50%, ≥75% and 100% responder status for PGTC seizure frequency during the first 12 weeks and the 24-week Treatment Period by treatment group will be provided.

Has been changed to:

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the first 6 weeks (Titration Period) compared to the Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the first 12 weeks of the Treatment Period compared to the Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTCS frequency during the Treatment Period compared to the Combined Baseline
- Percentage of subjects with at least a 75% reduction in PGTCS frequency during the first 6 weeks (Titration Period) compared to the Combined Baseline
- Percentage of subjects with at least a 75% reduction in PGTCS frequency during the first 12 weeks of the Treatment Period compared to the Combined Baseline
- Percentage of subjects with at least a 75% reduction in PGTCS frequency during the Treatment Period compared to the Combined Baseline

A histogram of ≥50%, ≥75%, and 100% (seizure freedom) responder status for PGTCS frequency during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

Section 8.3.2.5, Responder status – reduction in days with absence seizures, is new:

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in absence seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure days during the Treatment Period compared to the Prospective Baseline
- A histogram of ≥50%, ≥75%, and 100% (seizure freedom) responder status for reduction in days with absence seizures during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

Section 8.3.2.6, Responder status – reduction in days with myoclonic seizures

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in myoclonic seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure days during the first 6 weeks of the Treatment Period (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure days during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure days during the Treatment Period compared to the Prospective Baseline

Section 8.4.2.1, QOLIE-31-P variables, the following paragraph was added:

QOLIE-31-P data, for a specific visit may have a status of Abandoned if the subject doesn't complete the questionnaire. If the subject has duplicate QOLIE-31-P data for the same visit, where one record is deemed as Abandoned and one record is deemed as Completed, the Completed data will be used in the analysis and not the Abandoned record. All recorded QOLIE-31-P data will be listed.

Section 8.4.2.1, QOLIE-31-P variables, the following sentence was added to the 2nd paragraph:

The means of the QOLIE-31-P total score, subscale scores and health status item score will be plotted by visit.

Section 8.4.2.2, PedsQL variables, the following sentence was added:

The means of the PedsQL subscale scores and total score will be plotted by visit.

Section 8.4.2.3, EQ-5D-3L quality of life variables, the following sentence was added:

The mean of the EQ-5D-3L VAS will be plotted by visit. For the EQ-5D-3L, the percentage of subjects reporting a level within each dimension will be plotted in a histogram.

Section 10.1.2, Analysis of exposure variables, the 2nd paragraph was changed from:

Treatment duration will be summarized with the number and percentage of subjects with treatment duration by 3 Week categories: 1-21 days, 22–42 days, 43–63 days, 64–84 days, 85-105 days, 106–126 days, 127-147 days, 148-168 days, and > 168 days. Furthermore, the subject years exposed will be presented for the entire Treatment Period.

Has been changed to:

Treatment duration will be summarized with the number and percentage of subjects with treatment duration by 3 Week categories: 1 to 21 days, 22 to 42 days, 43 to 63 days, 64 to 84 days, 85 to 105 days, 106 to 126 days, 127 to 147 days, 148 to 168 days, and > 168 days. Furthermore, the subject years exposed will be presented for the entire Treatment Period.

If actual dosing information is presented, the LCM dose categories for oral solution are as follows: 0mg/kg/day/Unknown, >0 to <4mg/kg/day, ≥4mg/kg/day to <8mg/kg/day, and ≥8mg/kg day. The LCM dose categories for tablets are as follows: 0mg/day/Unknown, >0 to <200mg/day, ≥200 to <400mg/day, ≥400 to <600mg/day, ≥600 to 800mg/day, and ≥800mg/day.

Section 10.2, Adverse events, the following paragraphs were modified from:

- Incidence of other significant TEAEs (See Section 12.2 for details).

The following summary will be presented by actual dose at onset (Placebo oral solution, 0mg/kg/day, >0 to <4mg/kg/day, ≥4 to <8mg/kg/day, ≥8 to <12mg/kg/day, >12mg/kg/day, Placebo tablets, 0mg/day, >0 to <200mg/day, ≥200 to <300mg/day, ≥300 to <400mg/day and ≥400mg/day). AEs of pediatric subjects weighing <50kg randomized to LCM but where no LCM was taken will be summarized in the 0mg/kg/day column; AEs of adult subjects and pediatric subjects weighing ≥50kg randomized to LCM but where no LCM was taken will be summarized in the 0mg/day column. AEs of unknown dosing are not summarized but those taken where LCM dose is 0mg/kg/day or 0mg/day are in the applicable column. AEs of unknown dosing are those with UNK as the dose or known dosing and partial AE start or stop dates.

- Incidence of TEAEs by actual dose at onset

Subject data listings will be presented for the following:

- Subjects experiencing TEAEs
- Subjects experiencing Serious TEAEs
- Subjects experiencing TEAEs leading to discontinuation

A glossary of AEs will be presented showing the mapping of investigator terms to coded SOC and PTs.

A list of further AE tables required for EudraCT and clinicaltrials.gov is provided in Section 12.5.

Has been changed to:

- Incidence of other significant TEAEs (See Section 12.2.1 for details)
- Incidence of TEAEs for potential drug-induced liver injury (PDILI) (See Section 12.2.2 for details)

To assess TEAEs related to epilepsy, PTs will be identified by ongoing manual medical review. The following PTs (including those identified from continuing medical review) will be summarized: petit mal epilepsy, myoclonus, and myoclonic epilepsy.

- Incidence of TEAEs of interest related to epilepsy by 3-month exposure period of TEAE onset

The dose at onset TEAE summaries will be presented by the LCM dosing categories presented in Section 10.1.2. AEs of unknown dosing are those with no known dose or known dosing and partial AE start or stop dates.

- Incidence of TEAEs by actual dose at onset

Subject data listings will be presented for the following:

- Subjects experiencing adverse events on the ES
- Subjects experiencing Serious TEAEs on the SS
- Subjects experiencing TEAEs leading to discontinuation on the SS

A glossary of AEs will be presented showing the mapping of investigator terms to coded SOC and PTs.

A list of further AE tables required for EudraCT and clinicaltrials.gov is provided in Section 12.5.

Section 10.3, clinical laboratory evaluations, the following paragraphs were modified from:

Markedly abnormal (MA) values indicate significant deviations from the expected range of age-appropriate values. Marked laboratory abnormalities observed post-Baseline during the Treatment Period but not present at Baseline are considered treatment emergent. MA values for serum chemistry and hematology laboratory parameters are provided in UCB conventional (traditional) and standard units. The definition of MA values for hematology and chemistry values can be found in Section 12.3.

The number and percentage of subjects with at least 1 treatment-emergent markedly abnormal (TEMA) value will be summarized by visit for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified. TEMA values are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period. A table summarizing the number of subjects meeting the potential drug induced liver injury criteria will also be presented.

The NCI CTC criteria can be found in Section 12.4 . The number and percentage of subjects with treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher (hematology and clinical chemistry) will be summarized by treatment group, laboratory parameter, and visit for the Treatment Period. Treatment emergent abnormalities of grade 2 or higher are those that were observed during the Treatment Period at scheduled visits and not reporting a grade 2 or higher abnormality during the Baseline Period.

Has been changed to:

Treatment-emergent markedly abnormal (TEMA) values indicate significant deviations from the expected range of age-appropriate values. TEMA laboratory abnormalities results are those that are observed post-Baseline during the Treatment Period but are not present at Baseline. TEMA values for serum chemistry and hematology laboratory parameters are provided in UCB conventional (traditional) and standard units. The definition of MA values for hematology and chemistry values can be found in Section 12.3. The number and percentage of subjects with at least 1 TEMA value will be summarized by scheduled visit, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified. TEMA values are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period.

A table summarizing the number of subjects meeting the potential drug induced liver injury criteria will also be presented.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC) can be found in Section 12.4. The number and percentage of subjects with treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher (hematology and clinical chemistry) will be summarized by treatment group, laboratory parameter, and visit for the Treatment Period. Treatment emergent abnormalities of grade 2 or higher are those that were observed during the Treatment Period at scheduled visits and not reporting a grade 2 or higher abnormality during the Baseline Period. All treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher will be presented in a subject number listing.

Section 10.4.1, Vital Signs, the following sentence was inserted:

All TEMA results summarized will be presented in a subject number listing.

Section 10.4.2.2, Analysis of ECG parameters, was modified from:

Absolute values and change from Baseline of ECG parameters will be summarized using descriptive statistics for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the age groups. Unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values are listed.

The number and percentage of subjects who met each of the treatment-emergent abnormality criteria specified in Section 12.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval and QRS

interval. Subject numbers for those with treatment-emergent abnormal ECG values will be listed by abnormality criteria. Treatment-emergent abnormal results for a subject are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period.

Detailed information on the quantitative and qualitative ECG findings will be presented in subject data listings.

Has been changed to

For quantitative ECG measurements (heart rate, PR interval, QRS interval, QT interval, RR Interval and corrected QT intervals using Bazett and Fridiricia correction methods), summary statistics of the actual values and change from Baseline will be summarized using descriptive statistics for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the TEMA ECG criteria age categories. Last visit is the value from the last post baseline visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values are listed.

The number and percentage of subjects who met each of the TEMA criteria specified in Section 12.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval, QRS interval, QT interval and corrected QT intervals by scheduled visit and Last Visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit values during the Treatment Period. Subject numbers for those with TEMA ECG values will be listed by abnormality criteria. TEMA results for a subject are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period.

Detailed information on the quantitative and qualitative ECG findings will be presented in subject data listings.

Section 10.4.4.1, New Seizure Type, was modified from:

The incidence of new seizure types i.e. those not experienced in the Prospective Baseline but experienced during the Treatment Period as recorded in the diary will be summarized.

Has been changed to:

The number and percentage of subjects with seizure types present or absent in the Treatment Period vs whether the seizure type was present or absent in Combined Baseline will be tabulated. The number and percentage of subjects with seizure types present or absent in the Treatment Period vs whether the seizure type was present or absent in Seizure History (including Combined Baseline) will be tabulated.

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period with absence or myoclonic seizure type, respectively, indicated by the Seizure History Classification but not experienced in the Combined Baseline as recorded in the diary will be summarized.

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period but not experienced in the Combined Baseline or indicated in Seizure History Classification will also be summarized.

The number and percentage of subjects with new absence or myoclonic seizure types in the Treatment Period, with absence or myoclonic, respectively, indicated by the Seizure History Classification but not experienced in the Combined Baseline Period or subjects with ≥50% worsening in days with absence or myoclonic seizures, respectively, will be summarized.

Section 10.4.8.2, Analysis of Achenbach variables, the following sentence was added:

The means of the calculated T-score will be plotted by visit.

Section 10.4.9.1, BRIEF-P scores, the following sentence was added:

The means of the BRIEF-P assessment data will be plotted by visit.

Section 10.4.9.2, BRIEF scores, the following sentence was added:

The means of the BRIEF assessment data will be plotted by visit.

Section 12.2.1, Other Significant AEs, the table has been update with the latest criteria. Liver injury related criteria has been moved to the table in Section 12.2.2.

Section 12.2.2, AEs for Potentially Drug Induced Liver Injury, this table is newly added.

Section 12.3.4, Table 11, ECGs – Abnormality Criteria, categories for QT, QTc(F), and QTc(B) have been updated.

Section 12.5, Registry Required Tables, the list of tables required has been updated.

Section 12.6, Additional Subgroups to be programmed in ADSL, is newly added.

13.4 Amendment 4

13.4.1 Rationale for the amendment

A Type C Meeting request was submitted to FDA on Dec 12, 2018 to IND 057939 Sequence No. 1268 cross-reference IND 068407 and IND 073809. Included in the package was the SP0982 SAP Amendment 3. A Type C Written Response dated 4Mar2019 was received which prompted this amendment. Other items were clarified or added.

13.4.2 Modification and changes

At the request of FDA, the following items were added or clarified:

- New sensitivity analysis of the primary endpoint was added involving dropouts after 1st PGTCS
- Clarification regarding the checking of the proportional hazards assumption was added
- Variables and analyses involving reduction and increase in seizure frequency, responder status and worsening for absence and myoclonic seizures were added
- Analyses involving post-treatment vital sign and QTc measurements were added

The following items were clarified:

- Stratum pooling algorithm

- Algorithm for identifying rescue medications

The following items were added:

- A new listing of rescue medications
- References specific to the Cox proportional hazards analysis
- Additional analyses using the Development subgroup
- New variable identifying Asian sites

13.4.2.1 Specific changes

The information below was revised from:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017
Amendment #2	14 Mar 2017
Amendment #3	4 Jan 2019

Has been revised to:

SAP/Amendment Number	Date
Final SAP	09 Aug 2016
Amendment #1	24 Feb 2017
Amendment #2	14 Mar 2017
Amendment #3	4 Jan 2019
Amendment #4	26 Mar 2019

Section 3.2.5, the 3rd paragraph was changed from:

Benzodiazepines taken for rescue will be flagged with "RESCUE" in the indication field on the CRF, although rescue benzodiazepines will also be identified programmatically as any benzodiazepines taken intermittently for 1 day at any frequency. Rescue medication is defined as the intermittent use of benzodiazepines (limited to 2 doses per 28 days) for epilepsy indications if established at least 28 days prior to Visit 1. Lifetime benzodiazepines are defined as benzodiazepines taken in the subject's history and stopped at least 28 days prior to Visit 1.

Has been revised to:

Benzodiazepines taken for rescue will be flagged with "RESCUE" in the indication field on the CRF, although rescue AEDs will also be identified programmatically as any AED taken intermittently for 1 or 2 days, at any frequency, with an epilepsy or seizure related indication. Rescue medication is defined as the intermittent use of benzodiazepines (limited to 2 doses per 28 days) for epilepsy indications if established at least 28 days prior to Visit 1. Lifetime benzodiazepines are defined as benzodiazepines taken in the subject's history and stopped at least 28 days prior to Visit 1.

Section 3.9, the changes to protocol-defined analyses has been changed from:

For the key secondary efficacy variable, the Protocol Section 4.1.2 says that seizure freedom for PGTCS during the 24-week Treatment Period, will be estimated using Kaplan-Meier analysis.

The analysis of the key secondary endpoint has been clarified to assess the seizure-free rate using an extended Mantel-Haenszel technique which combines Kaplan-Meier estimates within each stratum. The extended Mantel-Haenszel technique is a randomization-based nonparametric method that provides a more robust method to assess seizure freedom.

Has been revised to:

For the key secondary efficacy variable, the Protocol Section 4.1.2 says that seizure freedom for PGTCS during the 24-week Treatment Period, will be estimated using Kaplan-Meier analysis. Also, Protocol Section 13.3.2.1 states that the key secondary efficacy variable will be analyzed in the same manner as the primary endpoint using the FAS and that the percentage of seizure-free subjects at 24 weeks will be estimated from the KM estimates of time to first seizure. The analysis of the key secondary endpoint has been clarified to assess the seizure-free rate at 24 weeks using an extended Mantel-Haenszel technique which combines Kaplan-Meier estimates within each stratum. The extended Mantel-Haenszel technique is a randomization-based nonparametric method that provides a more robust method to assess seizure freedom. Thus, the key secondary efficacy variable will not be analyzed in the same manner as the primary efficacy endpoint; the other secondary efficacy variable, time to first PGTCS, will be analyzed in the same manner as the primary efficacy endpoint.

Section 4.9, the stratum pooling algorithm has been updated from:

For the subjects with Baseline PGTCS frequency ≤2 per 28 days, the events for each of the 3 age at informed consent categories will be summed.

- If 2 of the age at informed consent categories combined have < 3 total events, then all age categories are combined for the analysis.
- If ≥4 to <12 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥12 and <18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the strata with the 2nd smallest number of events.

For the subjects with Baseline PGTCS frequency >2 per 28 days, repeat the same exercise to determine stratum pooling.

Has been revised to:

For the subjects with Baseline PGTCS frequency ≤2 per 28 days, the events for each of the 3 age at informed consent categories will be summed. For categories with < 3 total events, the combining should occur as follows:

- If 2 of the age at informed consent categories combined have < 3 total events, then all age categories are combined for the analysis.
- If ≥4 to <12 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.

- If ≥18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥12 and <18 years of age category.
- If ≥12 and <18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the strata with the 2nd smallest number of events.

Repeat the algorithm for combining strata for the subjects who did not have events if there are categories with < 3 total non-events.

For the subjects with Baseline PGTCS frequency >2 per 28 days, repeat the same exercise to determine stratum pooling for both events and non-events.

For each primary efficacy endpoint sensitivity analysis which uses stratum pooling, the pooling of the strata should be reassessed since the event distribution for the specific sensitivity may be different than the distribution in the primary efficacy endpoint analysis.

Section 6.6, the following sentence was added at the end of this section:

AEDs flagged as rescue medications will also be listed in subject data listings.

Section 8.1.2, the 2nd paragraph was revised from:

The hypothesis for the assessment of primary efficacy variable (time to event) is as follows:

$$H_0: \beta=0$$

Versus

$$H_1: \beta\neq 0$$

where β is the coefficient of an independent variable representing the treatment effect in the model. The hazard function is represented by

$$h(t,X) = h_0(t)\exp(\sum_{j=1}^{p}\beta_j X_j)$$

where x_j is the collection of independent variables and $h_0(t)$ is the baseline hazard at time t. For the null hypothesis, the testing will be 2-sided with an α=0.05; the p-value will be presented. The assumptions of proportional hazards will also be checked.

The stratified hazard ratio (HR) will be calculated using the placebo arm as the reference group. The SE and 95% CI for the HR will also be reported.

Has been revised to:

The hypothesis for the assessment of primary efficacy variable (time to event) is as follows:

$$H_0: \beta=0$$

Versus

$$H_1: \beta\neq 0$$

where β is the coefficient of an independent variable representing the treatment effect in the model. The hazard function is represented by

$$h(t,X) = h_0(t)\exp(\sum_{j=1}^{p}\beta_j X_j)$$

where x_j is the collection of independent variables and $h_0(t)$ is the baseline hazard at time t. For the null hypothesis, the testing will be 2-sided with an α=0.05; the p-value will be presented. The assumptions of proportional hazards will also be assessed graphically (e.g. log (log S) plot vs time, empirical score process) for any departure; non-proportionality is not expected when using a stratified Cox model. Depending on the departure from proportional hazards, a sensitivity analysis (e.g. piecewise proportional hazards, time-varying coefficient, restricted mean survival) may be performed.

The stratified hazard ratio (HR) will be calculated using the placebo arm as the reference group. The 95% CI for the HR will also be reported.

Section 8.1.4, the following sensitivity analysis was clarified from:

- Repeat the primary efficacy analysis using all PGTCS data (ie, all reported events) through each subject's first 166 days of treatment, on the FAS.

Was revised to:

- Repeat the primary efficacy analysis using all PGTCS data (ie, all reported events after the date of the 125th event) through each subject's first 166 days of treatment, on the FAS.

Section 8.1.4, the following sensitivity analysis was added:

- Repeat the primary efficacy analysis using the FAS, except all subjects who prematurely discontinue after their 1st PGTCS will be analyzed as treatment failures.

Section 8.2.2.2, the following sentence was clarified from:

The assumptions of proportional hazards will also be checked.

Was revised to:

The assumptions of proportional hazards will also be checked using the same approach as for the primary efficacy endpoint.

Section 8.3, was revised from:

All seizure data recorded during the treatment period will be summarized and listed for the seizure related other efficacy variables. Analyses of seizure-related other efficacy variables will be performed for the FAS.

Was revised to:

All seizure data recorded during the treatment period will be summarized and listed for the seizure related other efficacy variables. Analyses of seizure-related other efficacy variables will be performed for the FAS. For absence seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of absence seizures or reported absence seizures during baseline or the 24-week treatment period. For myoclonic seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of myoclonic seizures or reported myoclonic seizures during baseline or the 24-week treatment period.

Section 8.3.1.1, the following text was removed:

The percent change in log-transformed (PCHL) PGTCS frequency per 28 days from the Combined Baseline (CB) to the appropriate analysis period (T) is defined as:

PCHL = [(ln(SFT) – ln(SFCB)) / ln(SFCB)] x 100

where SFT corresponds to the 28-day PGTCS frequency during the relative period and SFCB corresponds to the 28-day Combined Baseline PGTCS frequency.

Section 8.3.1.2, paragraphs 3, 4, and 5 were revised from:

The percent change (PCH) in days with absence seizures per 28 days from the appropriate Baseline (B) to the appropriate analysis period (T) is defined as:

PCH = [(DT – DB) / DB] x 100

where DT corresponds to the number of days with absence seizures per 28 days during the relative period and DB corresponds to the number of days with absence seizures per 28 days during the Baseline Period. If DB is zero, then PCH will be missing and any such subjects will be excluded from the percent change summary. PCH will be calculated for the 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

Similarly, the percent change in the number of days with myoclonic seizures per 28 days from the appropriate Baseline Period will be calculated.

Were revised to:

The percent change (PCH) in days with absence seizures per 28 days from the Prospective Baseline (B) to the appropriate analysis period (T) is defined as:

PCH = [(DT – DB) / DB] x 100

where DT corresponds to the number of days with absence seizures per 28 days during the relative period and DB corresponds to the number of days with absence seizures per 28 days during the Prospective Baseline Period. If DB is zero, then PCH will be missing and any such subjects will be excluded from the percent change summary. PCH will be calculated for the 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

Similarly, the percent change in the number of days with myoclonic seizures per 28 days from the Prospective Baseline Period will be calculated.

Section 8.3.1.8, Variable: Days with absence and myoclonic seizures – worsening is new:

Safety of the LCM treatment will be based on the percent change in days with absence seizure per 28 days and days with myoclonic seizure per 28 days. The increase in days with absence seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period. The increase in days with myoclonic seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period.

Section 8.3.1.9, Variable: Absence and myoclonic seizure frequencies per 28 days is new:

In order to account for potential differences in the durations of the study periods for individuals, absence and myoclonic seizure data will be normalized to 28 days.

The 28-day absence SF will be calculated for the Prospective Baseline and Treatment Periods as:

SF =

(# absence seizures in the relative period/# days in relative period with evaluable absence seizure data)*28

The PCH in Absence seizure frequency per 28 days from the Prospective Baseline (PB) to the appropriate analysis period (T) is defined as:

PCH = [(SFT – SFPB) / SFPB] x 100

where SFT corresponds to the 28-day absence seizure frequency during the relative period and SFPB corresponds to the 28-day Prospective Baseline absence frequency; if subjects had no absence seizures in Prospective Baseline, then PCH cannot be calculated. PCH is calculated for 6-week Titration Period, first 12 weeks of the Treatment Period and the 24-week Treatment Period.

SF and PCH are calculated for subjects with myoclonic seizures using the same algorithm described above.

Section 8.3.1.10, Variable: Responder status – reduction in absence and myoclonic seizure frequencies is new:

Response to treatment will be based on the percent change in absence and myoclonic seizure frequencies, calculated as described in Section 8.3.1.9. A 50% responder is defined as a subject experiencing ≥50% reduction in absence (or myoclonic) seizure frequency per 28 days from the Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period). A 75% responder is defined as a subject experiencing ≥75% reduction in absence (or myoclonic) seizure frequency per 28 days from Prospective Baseline to the period of interest (6-week Titration Period, first 12 weeks of the Treatment Period or the 24-week Treatment Period).

Section 8.3.1.11, Variable: Absence and myoclonic seizure frequency - worsening is new:

Safety of the LCM treatment will be based on the percent change in absence seizure frequency per 28 days and myoclonic seizure frequency per 28 days. The increase in absence seizure frequency per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period. The increase in myoclonic seizure frequency per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% for the Treatment Period.

Section 8.3.2.5, the following last bullet was changed from:

A histogram of ≥50%, ≥75%, and 100% (seizure freedom) responder status for reduction in days with absence seizures during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

Was revised to:

A histogram of ≥50% and ≥75% responder status for reduction in days with absence seizures during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

Section 8.3.2.6, the following bullet was inserted:

A histogram of ≥50% and ≥75% responder status for reduction in days with myoclonic seizures during the first 6 weeks (Titration Period), first 12 weeks, and the 24-week Treatment Period by treatment group will be provided.

Section 8.3.2.7, Analysis: Percent change in absence and myoclonic seizure frequency per 28 days from Prospective Baseline is new:

Descriptive statistics will be provided on the percent change in absence and myoclonic seizure frequencies for the first 6 weeks of (entire Titration Period), first 12 weeks of, and the entire Treatment Period.

All absence and myoclonic seizure frequency per 28 days data will be listed.

Section 8.3.2.8, Analysis: Responder status – reduction in absence and myoclonic seizure frequency is new:

The following data will be summarized with descriptive statistics only:

- Percentage of subjects with at least a 50% reduction in absence seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure frequency during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure frequency during the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure frequency during the first 6 weeks (Titration Period) compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in myoclonic seizure frequency during the first 12 weeks of the Treatment Period compared to the Prospective Baseline
- Percentage of subjects with at least a 75% reduction in absence seizure frequency during the Treatment Period compared to the Prospective Baseline

Percentage of subjects with at least a 75% reduction in myoclonic seizure frequency during the Treatment Period compared to the Prospective Baseline

Section 10.2, the following TEAE summary was added:

- Incidence of common TEAEs for EU labeling (above or equal to reporting threshold of 1% (prior to rounding) of subjects in the total LCM group) and occurring >1% than in the placebo group

Section 10.4.4.4, Increase in absence seizure frequency is new:

Response to treatment regarding absence seizures will also be based on the percent change in the absence seizure frequency per 28 days, calculated as described in Section 8.3.1.9 . The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in absence seizure frequency per 28 days during the Treatment Period compared to the Prospective Baseline Period will be presented.

Section 10.4.4.5, Increase in myoclonic seizure frequency is new:

Response to treatment regarding myoclonic seizures will also be based on the percent change in the myoclonic seizure frequency per 28 days, calculated as described in Section 8.3.1.9. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in myoclonic seizure frequency per 28 days during the Treatment Period compared to the Prospective Baseline Period will be presented.

References were revised from:

Cox DR. Regression models and life-tables. J R Stat Soc Series B Methodol. 1972;34(2):187-220.

French JA, Temkin NR, Hammer AE, VanLandingham KE. Time to nth seizure analysis of lamotrigine as adjunctive therapy in subjects with primary generalized tonic-clonic seizures. Epilepsia. 2007;48(S6):77-78.

LaVange LM, Durham TA, Koch GG. Randomization-based nonparametric methods for the analysis of multicentre trials. Stat Methods Med Res. 2005;14:281-301.

Marcus R, Peritz E, Gabriel KR. On closed testing procedure with special reference to ordered analysis of variance. Biometrika. 1976;63:655-60.

Biton V, Di Memmo J, Shukla R, Lee YY, Poverennova I, Demchenko V, et al. Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study. Epilepsy & Behavior. 2010; 19: 352-8.

Was revised to the following:

Allison, PD. Survival Analysis Using SAS®: A Practical Guide. 2nd ed. Cary: SAS Institute; 2010

Biton V, Di Memmo J, Shukla R, Lee YY, Poverennova I, Demchenko V, et al. Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study. Epilepsy & Behavior. 2010; 19: 352-8.

Collett D. Modelling survival data in medical research. 3rd ed. London: CRC Press; 2015

Cox DR. Regression models and life-tables. J R Stat Soc Series B Methodol. 1972;34(2):187-220.

French JA, Temkin NR, Hammer AE, VanLandingham KE. Time to nth seizure analysis of lamotrigine as adjunctive therapy in subjects with primary generalized tonic-clonic seizures. Epilepsia. 2007;48(S6):77-78.

LaVange LM, Durham TA, Koch GG. Randomization-based nonparametric methods for the analysis of multicentre trials. Stat Methods Med Res. 2005;14:281-301.

Marcus R, Peritz E, Gabriel KR. On closed testing procedure with special reference to ordered analysis of variance. Biometrika. 1976;63:655-60.

SAS®/Stat 9.4: User's Guide. Cary: SAS Institute Inc; 2015

Section 12.3.3, Table 10 was updated with the post-treatment vital sign abnormalities requested in the Type C Written Response.

Section 12.3.4, Table 11 was updated with the post-treatment QTc abnormalities requested in the Type C Written Response.

Appendix 5: Registry Required Tables was revised from:

The following is the list of tables required for Article 41 (EudraCT), clinicaltrials.gov and/or Article 46 (European Pediatric Regulation). These tables will be produced at the same time as the CSR required Tables.

Disposition and Discontinuation Reasons by Development

Discontinuation due to AEs

Demographics by Development

Baseline Characteristics by Development

LCM Overall Exposure by Development

Study Medication Duration by Development

Incidence of TEAEs by Development – Overview

Incidence of TEAEs by Development

Incidence of Serious TEAEs by Development

Incidence of Non-serious TEAEs

Incidence of TEAEs by Relationship and Development

Incidence of TEAEs Leading to Discontinuation by Development

Incidence of Serious TEAEs by Relationship

Incidence of Non-serious TEAEs by Relationship

Incidence of Fatal TEAEs by Relationship

Incidence of Non-serious TEAEs Above Reporting Threshold of 5% of Subjects

Incidence of Non-serious TEAEs Above Reporting Threshold of 5% of Subjects by Relationship

Was revised to:

The following is the list of tables required for Article 41 (EudraCT), clinicaltrials.gov and/or Article 46 (European Pediatric Regulation). These tables will be produced at the same time as the CSR required Tables.

Disposition and Discontinuation Reasons by Development

Discontinuation due to AEs

Demographics by Development

Baseline Characteristics by Development

ILAE Seizure Classification History by Development

Classification of Epileptic Syndrome by Development

AEDs and Benzodiazepines at Study Entry by Development

Summary of Time to Second PGTCS by Development

Proportion of Subjects with Seizure Freedom at Day 166 by Development

PGTCS Frequency Observed Results and Percent Changes from Combined Baseline by Development

Absence Seizure Frequency Observed Results and Percent Changes from Prospective Baseline by Development

Myoclonic Seizure Frequency Observed Results and Percent Changes from Prospective Baseline by Development

Responder Status for PGCTS by Development

Responder Status for Absence Seizure Frequency by Development

Responder Status for Myoclonic Seizure Frequency by Development

Seizure-free Status for PGTCS by Development

Days with Absence Seizures Observed Results and Percent Changes from Prospective Baseline by Development

Increase in Days with Absence Seizures During the Treatment Period Compared to Prospective Baseline by Development

Increase in Absence Seizure Frequency During the Treatment Period Compared to Prospective Baseline by Development

Responder Status and Seizure Worsening for Days with Absence Seizures by Development

Days with Myoclonic Seizures Observed Results and Percent Changes from Prospective Baseline by Development

Increase in Days with Myoclonic Seizures During the Treatment Period Compared to Prospective Baseline by Development

Increase in Myoclonic Seizure Frequency During the Treatment Period Compared to Prospective Baseline by Development

Responder Status and Seizure Worsening for Days with Myoclonic Seizures by Development

Incidence of Absence Seizure Emergence or Worsening by Development

Incidence of Myoclonic Seizure Emergence or Worsening by Development

Seizure-free Status for All Generalized Seizure Types by Development

Study Medication Duration by Development

Cumulative Study Medication Duration by Development

Study Medication Daily Dosing by Development

Incidence of TEAEs by Development – Overview

Incidence of TEAEs by Development

Incidence of Serious TEAEs by Development

Incidence of Non-serious TEAEs

Incidence of TEAEs by Relationship and Development

Incidence of TEAEs Leading to Discontinuation by Development

Incidence of Serious TEAEs by Relationship

Incidence of Non-serious TEAEs by Relationship

Incidence of Fatal TEAEs by Relationship

Incidence of Non-serious TEAEs Above Reporting Threshold of 5% of Subjects

Incidence of Non-serious TEAEs Above Reporting Threshold of 5% of Subjects by Relationship

12-Lead ECG Summary by Development

Treatment-Emergent Abnormal 12-Lead ECG Findings for Subjects by Development

Section 12.6 was revised from:

The following subgroup variable will also be programmed:

Subjects enrolled at Japanese study sites (Japanese, non-Japanese)

Was revised to:

The following subgroup variable will also be programmed:

Subjects enrolled at Japanese study sites (Japanese, non-Japanese)

Subjects enrolled at Asian study sites (Asian, non-Asian) – Asian sites are those in Taiwan, South Korea, China and Japan

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

Approval Signatures

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Version: 3.0

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