STATISTICAL ANALYSIS PLAN

Study: SP0967

Product: Lacosamide

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN SUBJECTS WITH EPILEPSY ≥1 MONTH TO <4 YEARS OF AGE WITH PARTIAL-ONSET SEIZURES

SAP/Amendment Number	Date
Final SAP	07 Oct 2017
Amendment #1	05 Feb 2019
Amendment #2	07 May 2020

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADF	average daily frequency
AE	adverse event
AED	antiepileptic drug
ANCOVA	analysis of covariance
BMI	body mass index
BP	blood pressure
BRIEF®-P	Behavior Rating Inventory of Executive Function® - Preschool Version
CBCL	Child Behavior Checklist
CV	coefficient of variance
DAP	Data Analysis Plan
DBP	diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	electrocardiogram
eCRF	electronic Case Report Form
EEG	electroencephalogram
ER	emergency room
ETV	Early Termination Visit
FAS	Full Analysis Set
FAS-SDV	Full Analysis Set-Source Data Verified
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
ILAE	International League Against Epilepsy
IVRS	Interactive Voice Response System
LCM	Lacosamide
MA	markedly abnormal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
PDILI	Potential Drug Induced Liver Injury
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set

PT	preferred term
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
VNS	vagus nerve stimulation
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report for SP0967.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

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

2.1.2 Secondary objective

- To evaluate the safety and tolerability of LCM in subjects ≥1 month to <4 years of age with epilepsy who currently have uncontrolled partial-onset seizures.

2.1.3 Other objectives

- To evaluate the pharmacokinetics (PK) of LCM in children ≥1 month to <4 years of age.

2.2 Study variables

2.2.1 Efficacy variables

Primary and secondary efficacy variables will be based on video-electroencephalograms (EEGs) (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording).

2.2.1.1 Primary efficacy variable

For the US, the primary efficacy variable will be contingent on the percentage of subjects that discontinue from the study after the first dose of study medication but prior to performance of the End-of-Maintenance Period video-EEG (ie, early discontinuation).

The following variable will be considered primary for the US if ≤10% of subjects discontinue early from the study:

- The change in average daily frequency (ADF) of electrographic partial-onset seizures as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG

If >10% of subjects discontinue early from the study, the following contingency endpoint will be considered primary for the US (same as the primary efficacy variable for the EU):

- The proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG

For the EU:

- The primary efficacy variable will be the proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

2.2.1.2 Secondary efficacy variables

The secondary efficacy variables are described below.

- Percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG
- Proportion of subjects who achieved "seizure-free" status (yes/no) from all seizures, and from partial-onset seizure types only for subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG
- Proportion of subjects experiencing a ≥25% to <50%, 50% to 75%, or >75% reduction in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG
- Proportion of subjects experiencing no change in ADF of electrographic partial-onset seizures (between <25% reduction and <25% increase) from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG
- Proportion of subjects experiencing an increase in ADF of electrographic partial-onset seizures of ≥25% from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG

2.2.1.3 Other efficacy variables

Other efficacy variables to be examined include:

- Clinical Global Impression of Change at the end of the Maintenance Period
- Caregiver's Global Impression of Change at the end of the Maintenance Period
- Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) health summary score at the end of the Maintenance Period
- Healthcare resource use: concomitant medications, medical procedures, healthcare provider consultations not related to the study, and hospitalizations not related to the study

2.2.2 Pharmacokinetic/pharmacodynamic variables

Plasma concentrations of LCM will be obtained in order to:

- Develop a population PK model of LCM
- Investigate the correlation between LCM plasma concentrations and efficacy or safety

2.2.3 Safety variables

2.2.3.1 Primary safety variables

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

- Adverse events (AEs) reported spontaneously by the subject's parent(s) and/or legal representative(s)/caregiver(s) (in accordance with local regulation) or observed by the investigator
- Subject withdrawals due to AEs

2.2.3.2 Other safety variables

- Change in hematology and clinical chemistry parameters
- Change in 12-lead electrocardiograms (ECGs)
- Change in vital signs measurements (ie, blood pressure [BP] and pulse rate)
- Physical and neurological examination findings
- Changes in body weight, height, and calculated body mass index (BMI)

2.3 Study design and conduct

SP0967 is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM 8mg/kg/day to LCM 12mg/kg/day as adjunctive therapy in subjects ≥1 month to <4 years of age with epilepsy with partial-onset seizures.

The study is comprised of the following: a 7-day Baseline Period; a 20-day blinded Titration Period (with study medication dosing flexibility allowed based on tolerability) to attain the target dose of study medication for the 7-day blinded Maintenance Period (LCM 8mg/kg/day to LCM 12mg/kg/day, or matching placebo, with no adjustments to study medication dose allowed during the Maintenance Period), and a 12-day blinded Transition Period for subjects who complete the study and choose to enter the open-label extension study (EP0034) or a Taper Period (up to 16 days) followed by a 30-day Safety Follow-Up Period for subjects who are not eligible or who choose not to enter EP0034. The Transition Period will be required for eligible subjects who complete the Maintenance Period and choose to enter EP0034. The Taper Period and Safety Follow-Up Period are required for subjects who complete the study but choose not to enroll in EP0034 or for subjects who do not complete the Titration, Maintenance, and Transition Periods.

For each subject, the maximum total study duration can be up to 93 days (not withstanding visit windows), including the 30-day Safety Follow-Up Period. Each subject's participation in the study begins with a 7-day Baseline Period (no administration of study medication). Each subject's maximum total duration of study medication administration in SP0967 can be up to 55 days. This includes a 20-day Titration Period, a 7-day Maintenance Period, a 12-day Transition Period (for subjects who plan to enter the open-label extension study [EP0034]) and/or up to a 16-day Taper Period (for subjects who will not be entering EP0034).

The end of the study is defined as the date of the last visit of the last subject in the study.

A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized. Approximately 50% of the 244 randomized subjects should be <2 years of age. Of

these (n=122), every attempt will be made to enroll a minimum target of 20% (n=25) of subjects in each of the 3 age categories: ≥1 month to <6 months, ≥6 months to <1 year, and ≥1 year to <2 years.

Every attempt will be made to enroll subjects in the following age categories as detailed below:

- ≥1 month to <6 months of age (≥25 subjects)
- ≥6 months to <1 year of age (≥25 subjects)
- ≥1 year to <2 years of age (≥25 subjects)
- ≥2 years to <4 years of age (≥20 subjects)

Approximately 140 sites are planned in order to recruit the required subjects; additional sites will be added if deemed necessary.

The study will be conducted in North America, Europe, Asia Pacific, and Latin America with possible extension to other countries and regions. A target of approximately 30% of the randomized subjects should consist of subjects originating from sites in North America and Europe.

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

2.4 Determination of sample size

Assuming an effect size of 0.402, in which the effect size was calculated using a placebo-subtracted difference of -0.249 and a common standard deviation of 0.62 on the log-transformed data, the difference of -0.249 on the log-transformed data is equivalent to approximately 22% reduction over placebo after exponentiation. With this effect size, power of 80%, and a 2-sided test at the 5% level of significance, a sample of 99 subjects in each treatment arm will be needed.

Assuming a responder rate of 20% and 40% for the placebo and LCM groups, respectively, a 2-sided continuity corrected Chi-square test at a significance level of 5% will provide approximately 83% power with 99 subjects in the placebo group and 99 subjects in the LCM group.

Subjects are randomized into the study based on the initial interpretation of the video-EEG to meet study entry requirements. However, the subsequent detailed assessment of seizure types and counts needed for the efficacy analyses could lead to a discrepancy in seizure counts (ie, a subject initially thought to be eligible is later found to have fewer than the required number of partial-onset seizures during the End-of-Baseline Period video-EEG).To account for an anticipated difference of interpretation of the End-of-Baseline Period video-EEG of 5% as well as the potential subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.

2.4.1 Blinded sample size re-estimation procedure

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study, and have data available for analysis to check the validity of these assumptions using interim data from the study. The sample size re-estimation with equal allocation in each arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011). An assessment of the observed dropout rate will

also be made as part of this analysis, and the potential dropout rate of 14% used for calculation of the initial sample size will be modified based on the observed rate. Additionally, an assessment of the observed difference of End-of-Baseline Period video-EEG interpretation rate will be made; the anticipated rate of 5% will be modified based on the observed rate.

The final sample size will be modified according to the sample size re-estimate and also the anticipated dropout rate and anticipated rate of difference of interpretation of the End-of-Baseline Period video-EEG; however, an upper bound will be applied to reach a maximum sample size based on practical and logistical considerations. The initial sample size re-estimate using Guenther adjustment will not be adjusted above 109 subjects per treatment arm, the original estimated overall study dropout rate will not be adjusted above 24%, and the difference of End-of-Baseline Period video-EEG interpretation rate will not be adjusted above 10%.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

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

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. The denominator for all percentages will be the number of subjects in the treatment group within the analysis set of interest, unless otherwise noted.

For continuous parameters, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.

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

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

In general, the maximum number of decimal places reported should be 4 for any summary statistics.

Confidence intervals (CIs) will be presented to 1 more decimal place than the original data.

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999." Statistical comparison will be performed at the 0.05 level of significance.

A complete set of listings containing all documented data and all calculated data (eg, change from Baseline) will be generated, and will be sorted by site, subject number and visit (where applicable).

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Last dose of study medication

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

3.2.1.2 Relative day

Relative day will be calculated as the current date minus the date of first dose of study medication plus 1 for days on or after the day of first dose of study medication and prior to or on the day of last study medication dose (eg, the day of first dose will be Day 1). For days prior to the first dose of study medication (the day prior to first dose will be Day -1), relative day will be calculated as the current date minus the date of first dose of study medication. For days after the last dose of study medication, relative day will be calculated as the current date minus the date of last dose of study medication including a "+" to denote post-treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial or missing dates.

3.2.2 Study periods

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

Baseline Period

This is defined as the period from the date of Visit 1 (entry to study) to 1 day prior to the date of first dose of study medication. In addition, pre-dose scheduled assessments which are performed on the date of first dose of study medication will be assigned to the Baseline Period. Any unscheduled assessments which are performed prior to the date of first dose of study medication will also be assigned to the Baseline Period.

Titration Period

This is defined as the period of time from the date of first dose of study medication to the last Titration Period visit date (Telephone Contact 3 [T3]) for subjects who complete the Titration Period, or from the date of first dose of study medication to the date of the Early Termination Visit (ETV) for subjects who prematurely discontinue prior to the last Titration Period visit date (T3). If a subject does not have a T3/ETV, then either the date of the last scheduled or unscheduled visit during the Titration Period or the date of last known dose of study medication, if this is after the last scheduled or unscheduled visit date during the Titration Period, will define the end date of the Titration Period.

Maintenance Period

This is defined as the period of time from the day after the end date of the Titration Period (T3) to the last Maintenance Period visit date (Visit 6 [Day 27]) for subjects who complete the Maintenance Period, or from the day after the end of the Titration Period (T3) to the date of the ETV for subjects who prematurely discontinue prior to the last Maintenance Period visit date (Visit 6 [Day 27]). If a subject does not have a Visit 6 (Day 27)/ETV, then either the date of the last scheduled or unscheduled visit during the Maintenance Period or the date of last known dose of study medication, if this is after the last scheduled or unscheduled visit date during the Maintenance Period, will define the end date of the Maintenance Period.

Treatment Period

This is defined as the period of time from the date of first dose of study medication to the last Treatment Period visit date (Visit 6 [Day 27]) for subjects who complete the Treatment Period, or from the date of first dose of study medication to the date of the ETV for subjects who prematurely discontinue prior to the last Treatment Period visit date (Visit 6 [Day 27]). If a subject does not have a Visit 6 (Day 27)/ETV, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of study medication, if this is after the last scheduled or unscheduled visit date during the Treatment Period, will define the end date of the Treatment Period.

Transition Period

For those subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034), the Transition Period is defined as the date after the end of the Maintenance Period (Visit 6 [Day 27]) to the date of Transition Visit 2.

Taper Period

For those subjects who discontinue study medication or for those subjects who complete the Maintenance Period but choose not to enter EP0034, the Taper Period is defined as the date after the end of the Titration, Maintenance or Transition Period, whichever is later, to the date of the Taper Visit.

Safety Follow-Up Period

There will be a 30-day Safety Follow-Up Period for subjects not entering EP0034. The start of the Safety Follow-Up Period is defined as the day after the last dose of study medication in SP0967 and continues until the date of last telephone contact and/or 30 days after the last dose of study medication, whichever is later.

3.2.3 Mapping of assessments performed at Early Termination Visit

Efficacy and safety assessments at an ETV that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the ETV if the assessment was scheduled to occur at that visit. Such assessments will also be considered for Last Visit.

3.2.4 Study visit labeling

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

- "Baseline"

- "Visit X (Day X)" for scheduled visits during the Treatment Period
- "Transition Visit X" for scheduled visits during the Transition Period
- "Taper Period"
- "Safety Follow-up Period"
- "Last Visit" (see below in Section 3.2.5 for further information)

Listings will also include "Unscheduled Visit" as applicable.

3.2.5 Last visit

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

3.2.6 Exposure duration

The overall duration of LCM exposure for each subject will be calculated as the date of the last dose of LCM minus the date of the first dose of LCM plus 1 day. Gaps in treatment or days with unknown dosing will not be subtracted from the duration of exposure.

3.2.7 Age, age categorization, age at first diagnosis, epilepsy duration

For subjects who do not have a full date of birth reported based on region-specific regulations, age in years and months will be obtained from the Interactive Voice Response System (IVRS) used to randomize subjects. Otherwise, age will be calculated relative to the date of informed consent with the following formula:

(Date of informed consent – date of birth) / 365.25.

Age in years and months obtained from the IVRS will be used to derive separately, age in months (integer) and age in years (2 decimal places), as follows:

Age (months) = IVRS age (months) + (IVRS age [years] x 12)

Age (years) = IVRS age (years) + (IVRS age [months] / 12)

The age at first diagnosis will be given in years and will be derived applying all rules for missing date imputation (see Section 4.2.5) with the following formula:

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

Epilepsy duration (years) will be calculated as:

(Date of informed consent – date of first diagnosis of epilepsy) / 365.25.

Age group categories are as reported in the eCRF and are as follows:

- ≥1 to <6 months
- ≥6 months to <1 year
- ≥1 to <2 years
- ≥2 to <4 years

3.2.8 Body Mass Index (BMI)

BMI will be calculated as follows using height and weight at Visit 1; if weight is missing at Visit 1 then weight at Visit 2 will be used:

BMI = weight (kg) / (height [m])^2

3.2.9 Electrographic partial-onset seizures

Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.

The video-EEG recordings will be evaluated locally by the investigator, sub investigator, or qualified designated reader. Subjects who discontinue on or before Day 20 will not require an End-of-Maintenance Period video-EEG.

For the purposes of this SAP, the term electrographic partial-onset seizures will be used to define electrographic partial-onset seizures with or without clinical correlate; electrographic and electroclinical partial-onset seizures will be included for subjects aged ≥1 month to ≤6 months, and electroclinical partial-onset seizures will be included for subjects aged >6 months to <4 years.

Infants aged ≥1 month to ≤6 months

Partial-onset seizure frequency for infants aged ≥1 month to ≤6 months will be based on electrographic seizures.

The total number of partial-onset seizures is calculated as the total number of type IA/IB electrographic seizures plus the total number of type IA/IB electroclinical seizures plus the total number of type IC seizures.

The total number of seizures is calculated as the total number of partial-onset seizures (as defined above) plus the total number of other seizure types reported.

Infants aged >6 months to <4 years

Partial-onset seizure frequency for infants aged >6 months to <4 years will be based on electrographic seizures with an accompanying clinical correlate.

The total number of partial-onset seizures is calculated as the total number of type IA/IB electroclinical seizures plus the total number of type IC seizures.

The total number of seizures is calculated as the total number of partial onset seizures (as defined above) plus the total number of other seizure types reported.

Calculation of the End-of-Baseline Period ADF of electrographic partial-onset seizures will be based on the results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) at Visits 2 and 3. The End-of-Maintenance Period ADF of electrographic partial-onset seizures will be based on results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) at Visit 6.

3.2.10 ADF of Electrographic partial-onset seizures

The ADF of electrographic partial-onset seizures will be calculated as (number of partial-onset seizures as recorded on the video-EEG divided by the number of interpretable hours recorded) multiplied by 24.

3.2.11 Absolute change in ADF of electrographic partial-onset seizures

The change in ADF of electrographic partial-onset seizures is calculated as the ADF of electrographic partial-onset seizures from the End-of-Maintenance Period video-EEG minus the ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG.

3.2.12 Percent change in ADF of electrographic partial-onset seizures

The percent change in ADF of electrographic partial-onset seizures is calculated as the ADF of electrographic partial-onset seizures from the End-of-Maintenance Period video-EEG minus the ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG divided by the ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG and then multiplied by 100.

3.2.13 Percent reduction in ADF of electrographic partial-onset seizures

The percent reduction in ADF of electrographic partial-onset seizures is calculated as the ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG minus the ADF of electrographic partial-onset seizures from the End-of-Maintenance Period video-EEG divided by the ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG and then multiplied by 100.

3.2.14 Response to treatment

Response to treatment is based on the percent reduction in ADF of electrographic partial-onset seizures. Subjects who experience 50% or greater reduction in their electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline video-EEG will be considered a responder.

3.2.15 Seizure-free status

At least 48 hours of interpretable recordings during the End-of-Maintenance Period video-EEG is required to determine a subject's seizure-free status. As above, the term electrographic partial-onset seizures will be used to define electrographic partial-onset seizures with or without clinical correlate; electrographic and electroclinical partial-onset seizures will be included for subjects aged ≥1 month to ≤6 months, and electroclinical partial-onset seizures will be included for subjects aged >6 months to <4 years

<u>All seizures</u>

A subject is considered seizure free from all seizures if the End-of-Maintenance Period video-EEG has 0 (zero) seizures reported, that is, from all seizure types not just partial-onset seizure types.

<u>Partial-onset seizures</u>

A subject is considered seizure free from partial-onset seizures if the End-of-Maintenance Period video-EEG has 0 (zero) partial-onset seizures reported.

3.2.16 Pediatric Quality of Life inventory (PedsQL)

The PedsQL is a validated instrument that consists of generic core scales suitable for use of pediatric population, including those with acute or chronic health conditions. The PedsQL Measurement Model consists of developmentally appropriate forms of pediatric subjects ≥1 month to ≤12 months, ≥13 month to ≤24 months, and >2 years to ≤4 years. For each subject, the same version of the PedsQL used at Visit 3 (Baseline) should be maintained for the duration of the study.

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

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

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

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

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

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

The above algorithm will also be used to calculate an overall total scale score (all scales), the psychosocial health summary score (a combination of the emotional, social, and cognitive functioning questions), and the physical health summary score (a combination of the physical functioning and physical symptoms questions) for each subject ≤24 months of age, and an overall total scale score (all scales), the psychosocial health summary score (a combination of the emotional, social, and school functioning questions), and the physical health summary score (the physical functioning questions) for each subject >2 years age.

3.2.17 Hospital stay duration

The duration of each hospital stays (in days) will be calculated as the discharge date minus the admission date (Hospitalization/Emergency Room [ER] Visit Date on the eCRF module) plus 1 day for hospital stays with a discharge date.

3.3 Definition of Baseline values

Unless otherwise specified, Baseline will be defined as the last non-missing value prior to the first dose of study medication, including pre-dose scheduled assessments on the date of Visit 3.

For ECGs, Baseline is defined as the average of all interpretable ECG measurements taken prior to date of first dose of study medication. If no ECGs are available prior to the first dose of study medication, Baseline will not be defined for ECG assessments.

Baseline assessment of seizure data will be based on seizure data collected at Visits 2 and 3.

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 separately in an important protocol deviations document. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

In general, protocol deviations will be considered according to the following general categories:

- Inclusion criteria
- Exclusion criteria
- Withdrawal criteria
- Prohibited concomitant medications
- LCM dosing regimen
- Procedural non-compliance

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

In addition, protocol deviations related to the impact of the global pandemic of novel coronavirus (COVID-19) will be identified, reviewed, and agreed upon prior to unblinding of the database.

3.5 Analysis sets

3.5.1 Safety Set

The Safety Set (SS) will include all randomized subjects who took at least 1 dose of study medication. This is the primary analysis set for the safety variables.

3.5.2 Full Analysis Set

The primary analysis set for the efficacy data will be the Full Analysis Set (FAS), which will include all subjects in the SS.

3.5.3 Full Analysis Set – Source Data Verified

The Full Analysis Set-Source Data Verified (FAS-SDV) will include all subjects in the FAS who have both their End-of-Baseline Period and End-of-Maintenance Period video-EEG eCRF pages source data verified using on-site monitoring processes.

3.5.4 Per Protocol Set

The secondary analysis set for the efficacy data will be the Per Protocol Set (PPS), which includes all subjects in the FAS who did not have important protocol deviations related to efficacy.

3.5.5 Pharmacokinetic Per Protocol Set

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

3.6 Treatment assignment and treatment groups

At Visit 3, subjects will be randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or placebo in a 1:1 ratio. Randomization will occur after completion of the End-of-Baseline video-EEG and after confirmation that the subject has met selection criteria. Randomization will be stratified by age category (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age).

Where specified in this SAP, data will be summarized by treatment group (LCM versus placebo).

3.7 Center pooling strategy

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

3.8 Age strata pooling strategy

It may be necessary to appropriately pool randomization age stratification categories for the primary efficacy analysis and planned sensitivity analyses. The final strategy for pooling will be determined at the final DEM prior to unblinding the study.

3.9 Coding dictionaries

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

3.10 Changes to protocol-defined analyses

For sensitivity analyses requiring multiple imputation, missing data multiple imputation will not be performed by treatment group and age group (≥1 month to < 6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age). Multiple imputation will instead be performed by treatment group adjusting for age group.

For analyses of LCM plasma concentrations, in addition to summarizing descriptive statistics as described in the protocol, all tabulations will be performed by LCM maintenance dose level and separately by LCM maintenance dose level and age group.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The primary efficacy analysis and planned sensitivity analyses will be adjusted for log-transformed Baseline seizure ADF, age category (4 age stratification categories, pooled as appropriate) and center (appropriately pooled) in the analysis of covariance (ANCOVA) models. Other statistical models may be adjusted for covariates, and any such adjustments will be described in the context of the analyses performed.

4.2 Handling of dropouts or missing data

4.2.1 Missing data

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

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to treatment per the investigator will be assumed to be related. It is not expected that events will have missing seriousness, but if they do, seriousness will not be imputed and will be left as missing. Incomplete or missing dates for events will be handled as described in Section 4.2.2.

4.2.2 Incomplete dates for adverse events and concomitant medications

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or medications will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

- Missing start day, but month and year present:

  If the start of treatment occurred in the same month and year as the occurrence of the AE/medication, the start day of the event/medication will be assigned to the day of first dose of study medication. Otherwise the start day will be set to the 1st day of the month.

- Missing start day and month, but year present:

  If the start of treatment occurred in the same year as the occurrence of the AE/medication, the start day and month will be assigned to the date of first dose of study medication. Otherwise the start day and month will be set to January 1st.

- Missing end day, but month and year present:

  The end day will be set to the last day of the month.

- Missing end day and month, but year present:

The end day and month will be set to the maximum of the date of study termination or the date equivalent to 30 days after last dose of study medication.

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

4.2.3 Definition of concomitant medication in case of missing dates

With respect to definition of medication as concomitant, the following rule will be applied in case of completely missing stop and/or start date information:

Medications with a missing start date whose stop date is either unknown or after the date of the first dose of study medication, will be considered as concomitant medication, but not as prior medication. Medications with a missing start date whose stop date is prior to the date of first dose of study medication will be considered as prior medication, but not as concomitant medication. Medications with a missing stop date and a start date prior to the data of last dose of study medication will be considered as concomitant medication.

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

4.2.4 Incomplete dates for the last administration of study medication

For purposes of imputing missing components of partially reported dates for the last administration of study medication, the algorithms listed below will be followed. Stop dates of study medication will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

- Missing last administration day, but month and year present:

  The last administration day will be set to the last day of the month or the date of the final contact, whichever is earlier in the month.

- Missing last administration day and month, but year present:

  The last administration day will be set to the last day of the year or the date of the final contact, whichever is earlier in the year.

- Completely missing date of last administration:

  For calculating the duration of exposure, if the date of last administration is completely missing and no information could be obtained from data cleaning exercises, the date of last administration should be imputed as the date of last contact according to the Study Termination eCRF module. For all other purposes, no imputation will be done if the date of last administration is completely missing.

If a subject died during the study, and the imputed last administration date according to the rules above is after the date of death, the last administration date will be assigned to the date of death.

4.2.5 General imputation rule for incomplete dates

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of AEs
- Start and stop dates of concomitant medication
- Start and stop dates of study medication

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

For calculation of date of diagnosis and duration of diagnosis the following rules will be used for imputation of incomplete dates:

If the month and year are available, the diagnosis date is imputed as the later of the following dates: the first day of the month, the subject's birthdate, or the date of the first seizure (if available). If only a year is available, the later of the following dates will be imputed: January 1st of the year, the subject's birthdate, and the date of the first seizure.

4.3 Interim analyses and data monitoring

No formal interim analysis for determination of efficacy is planned for this study. To ensure subject safety, interim reviews of safety data will be performed using an Independent Data Monitoring Committee (IDMC). Serious adverse events and other significant events are monitored and will be triaged by the medical monitor and UCB Drug Safety in real time. After this triage, events will be passed on to the IDMC as appropriate. In addition, 3 interim reviews of safety data by the IDMC are planned when 25%, 50%, and 75% of subjects have been randomized and at study completion. Study enrolment will not be halted during planned IDMC review of the safety data. The objective, procedures, and timing of IDMC safety assessments to evaluate risk and benefit for subjects in SP0967 will be described in the IDMC Charter.

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study (including those who discontinued), and have data available for analysis to check the validity of the assumptions used for determining the sample size using interim data from the study.

4.4 Multicenter studies

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

Treatment by center interactions will not be explored in the analysis, but center (appropriately pooled) will be included as a factor in the primary efficacy analysis and planned sensitivity analyses.

4.5 Multiple comparisons/multiplicity

There will be no adjustment for multiplicity in this study.

4.6 Use of an efficacy subset of subjects

The FAS, defined in Section 3.5.2, is the primary analysis set for the efficacy analyses.

The primary and secondary efficacy analyses will be repeated on the FAS-SDV, defined in Section 3.5.3.

The primary efficacy analyses will be repeated on the first 244 subjects enrolled in the study for the FAS and FAS-SDV. The first 244 subjects enrolled in the study will be determined using the date of informed consent. In case of ties, date of randomization will be used.

The PPS is the secondary analysis set for the efficacy analyses.

4.7 Active-control studies intended to show equivalence

This section is not applicable for this study.

4.8 Examination of subgroups

Age groups as defined in Section 3.2.7 will be used within summaries of disposition, demography, exposure and adverse events.

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

Descriptive summaries of US and EU primary efficacy endpoints will be provided by age group and treatment group.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects screened, and the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure will be presented by age group and overall. Screen failures are allowed to be re-screened after consultation with the medical monitor. Subjects who are re-screened and subsequently enrolled and randomized are not included in screen failure counts. These subjects will be provided in a listing with previous subject ID and date of re-screening.

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

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

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

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

The number and percentage of subjects screened under each protocol amendment (estimated by date of informed consent) will be presented. This will also be presented in the subject data listings.

5.2 Protocol deviations

Important protocol deviations defined in the important protocol deviations document, and additionally identified at the DEMs before unblinding of the database, will be listed. In addition, the number and percentage of subjects with at least 1 important protocol deviation will be summarized overall and by category of important protocol deviation for the SS. The number and percentage of subjects with no important protocol deviations will also be summarized for the SS.

An additional listing of protocol deviations related to the impact of the global pandemic of novel coronavirus (COVID-19) will be provided.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographic variables will be presented by treatment group and overall for the SS and repeated by treatment group and age group using the levels defined in Section 3.2.7. The variables to be considered are:

- Age (months) and age groups (as defined in Section 3.2.7)
- Age (years) (as defined in Section 3.2.7)
- EudraCT age category (28 days to <24 months, ≥24 months to <12 years)
- Gender
- Weight (kg) at Visit 1, if missing, weight (kg) at Visit 2
- Height (cm)
- BMI (kg/m2) (as defined in Section 3.2.8)
- Head circumference (cm)
- Racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other/Mixed)
- Ethnicity (Hispanic or Latino, and not Hispanic or Latino)
- Region (North America, Latin America, Western Europe, Eastern Europe, Asia/Pacific/Other)
- Country (Argentina, Brazil, China, Croatia, Czech Republic, France, Georgia, Greece, Hungary, Israel, Italy, Lithuania, Mexico, Philippines, Poland, Portugal, Republic of Moldova, Republic of Korea/South Korea, Romania, Russia, Serbia, Taiwan, Thailand, Ukraine, US)
- Center Pool (as determined at the final DEM prior to unblinding the study)
- Vagus nerve stimulation (VNS) use (Active VNS, No VNS, VNS not active) at Visit 1

6.2 Medical history and concomitant diseases

The number and percentage of subjects with a medical history condition (except epilepsy), including both resolved and ongoing conditions at the time of study entry, will be summarized

overall and by MedDRA® primary system organ class (SOC) and preferred term (PT) by treatment group for the SS.

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

6.3 History of epilepsy

6.3.1 History of seizure types

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

A subject will be classified as having a history of partial-onset seizures if the subject has a history of simple partial (type IA), complex partial (type IB), or partial, secondary generalized (type IC) seizures. Similarly, a subject will be classified as having a history of generalized seizures if the subject has a history of absence (type IIA1), atypical absence (type IIA2), myoclonic (type IIB), clonic (type IIC), tonic (type IID), tonic-clonic (type IIE) or atonic (type IIF) seizures. A subject will be classified as having a history of unclassified epileptic seizures if the subject has a history of type III seizures.

6.3.2 History of seizure characteristics

History of epileptic seizures, including the number and percentage of subjects with a history of withdrawal seizures and percentage with a history of status epilepticus will be summarized. In addition, quantitative summaries of epilepsy duration and age at diagnosis (as defined in Section 3.2.7) will be summarized for the SS.

6.3.3 Historical seizure count

The Historical Seizure Count eCRF records the number of seizures per pre-selected ILAE seizure code experienced by the subject during the 2 weeks prior to screening visit. These data will be provided in a subject data listing.

6.4 Prior and concomitant medications

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

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

6.4.1 Number of Previous AEDs

The number of previous AEDs defined as AEDs taken and stopped >14 days prior to Visit 1 (ie, prior to entry into the Baseline Period), and not taken during the course of the study, will be summarized by treatment group and overall for the SS based on the following categorization: 0 AEDS, 1 to 3 AEDs, 4 to 6 AEDs, and ≥7 AEDs.

6.4.2 AEDs taken prior to the Baseline Period

The number and percentage of subjects taking AEDs prior to the Baseline Period defined as AEDs with a start date prior to the date of informed consent, ie, prior to entry to the Baseline Period, excluding previous AEDs, will be summarized by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

6.4.3 AEDs taken during the Baseline Period

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

6.4.4 AEDs taken on day of first dose of study medication

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

The number and percentage of subjects taking AEDs on the day of first dose of study medication, excluding AEDs taken as rescue medication, will be summarized by WHODD chemical subgroup (Level 4) and preferred drug name, and by treatment group and overall for the SS.

6.4.5 Concomitant AEDs

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

Concomitant AEDs will be defined by a manual review of all unique combinations of ATC codes and indications reported in the database to identify medications taken to treat epilepsy.

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

6.4.6 Non-AEDs taken prior to the Baseline Period

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

6.4.7 Non-AEDs taken during the Baseline Period

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

6.4.8 Concomitant Non-AEDs

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

7 MEASUREMENTS OF TREATMENT COMPLIANCE

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

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

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

Where:

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

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

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

Where:

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

Baseline weight is the most recent IVRS weight reported before a subject is dosed.

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

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

A subject's dosing compliance should be within 75 to 125% during each period. Compliance to study medication dosing will be calculated for the overall Treatment Period (Titration + Maintenance Periods).

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

8 EFFICACY ANALYSES

The analyses of the primary and secondary efficacy variables are based on the ADF of electrographic partial-onset seizures (defined in Sections 3.2.9 and 3.2.10).

Other efficacy variables include the Clinical Global Impression of Change, the Caregiver's Global Impression of Change, and quality of life assessments (PedsQL and health care resource use).

All study efficacy variables will be summarized for the FAS by treatment group unless specified otherwise.

8.1 Statistical analysis of the primary efficacy variable(s)

8.1.1 Primary efficacy variable(s)

The primary and secondary efficacy variables are based on the ADF of partial-onset seizures as measured on video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording).

8.1.1.1 Primary efficacy variable for the US

For the US, the primary efficacy variable is contingent on the percentage of subjects that discontinue from the study after the first dose of study medication but prior to performance of the End-of-Maintenance Period video-EEG (ie, early discontinuation).

The following variable is considered primary for the US if ≤10% of subjects discontinue early from the study:

- The change in ADF of electrographic partial-onset seizures as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG

If >10% of subjects discontinue early from the study, the following contingency endpoint is considered primary for the US (same as the primary efficacy variable for the EU in Section 8.1.1.2):

- The proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG

8.1.1.2 Primary efficacy variable for the EU

For the EU, the primary efficacy variable is the proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

8.1.2 Primary analysis of the primary efficacy variables

8.1.2.1 Primary analysis of the primary efficacy variable for the US

Contingent upon ≤10% of subjects discontinuing early from the study, the primary efficacy variable for the US is the change in ADF of electrographic partial-onset seizures during the Maintenance Period compared to the end of the Baseline Period.

Seizure ADF will be analyzed using an ANCOVA with terms for treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF and ln refers to the natural log. Log-transformed Baseline seizure ADF will be used as a covariate.

The seizure ADF between LCM and placebo will be compared using least squares means (LSMs). The percent reduction over placebo will be estimated as 100 x (1 – exp [LSM_{LCM} – $LSM_{placebo}$]). The pairwise comparisons of LCM treatment versus placebo for analyzing the reduction in seizure frequency described above will be performed at the two-sided 5% level of

significance. The treatment estimates (LSMeans and 95% CIs) will be back-transformed using the exponential function and subtracting 1.

The analysis of this efficacy variable will consist of all subjects in the FAS who have at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Assumptions for the parametric model described above will be evaluated by diagnostic (eg, Shapiro-Wilk test for normality) and graphical methods such as residual plots, including normal probability plots, histograms, and plots of residuals versus Baseline covariate values and treatment. An assessment will be made with regards to the influence of individual observations (eg, extreme outliers) on the analysis. To the extent feasible, such potential influential observations will be identified prior to unblinding, and an assessment will be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If deemed that a non-parametric method is warranted, an ANCOVA model on rank of seizure ADF with terms for age group, treatment and center (pooled appropriately) will be employed for the primary analysis. Ranked Baseline seizure ADF will be used as a covariate.

Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy variable for the US is identical to the primary efficacy variable for the EU, described in Section 8.1.1.2.

Whichever of these efficacy variables are not designated as the primary efficacy variable will still be summarized as a secondary efficacy variable.

8.1.2.2 Primary analysis of the primary efficacy variable for the EU

The primary efficacy variable for the EU is the proportion of responders during the Maintenance Period. Subjects with a 50% or more reduction in seizure ADF will be categorized as responders. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG. Subjects who withdraw or drop out before the first 48 hours of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non-responders and will be included in the analysis; all other subjects will be missing and will not be included in this analysis.

Subjects with 0 seizures at Baseline will be missing their Percent Change from Baseline. Subjects with 0 seizures at Baseline will be considered non-responders.

The proportion of responders between LCM and placebo will be analyzed using logistic regression with treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately) as factors. From this model, odds ratios will be presented along with the corresponding 95% CI and p-value. In addition, the number and percentage of subjects with a 50% or more reduction in seizure ADF will be presented by treatment group and age group.

8.1.3 Sensitivity analyses of the primary efficacy variables

For sensitivity analyses that are applied to subjects who discontinued early, the population will include all subjects with at least 48 interpretable hours of EEG data at both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, and additionally all subjects

with at least 48 interpretable hours of End-of-Baseline Period video-EEG and missing status for End-of-Maintenance Period video-EEG as a consequence of early discontinuation.

8.1.3.1 Sensitivity analyses of the primary efficacy variable for the US

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of modified data cleaning and reconciliation processes, early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

- Repeat the primary analysis for the PPS.
- Repeat the primary analysis for the FAS-SDV.
- Repeat the primary analysis for the first 244 subjects enrolled in the study for the FAS.
- Repeat the primary analysis for the first 244 subjects enrolled in the study for the FAS-SDV.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using the Baseline observation-carried-forward approach. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced by the overall mean ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG from the subject's respective treatment group. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis for the FAS for all subjects who have at least 24 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG (rather than at least 48 hours).

8.1.3.2 Sensitivity analyses of the primary efficacy variable for the EU

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of modified data cleaning and reconciliation processes, early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

- Repeat the primary analysis for the PPS.

- Repeat the primary analysis for the FAS-SDV.
- Repeat the primary analysis for the first 244 subjects enrolled in the study for the FAS.
- Repeat the primary analysis for the first 244 subjects enrolled in the study for the FAS-SDV.
- Repeat the primary analysis for the FAS, except subjects who discontinued from the study prior to performance of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will still be considered non-responders, and subjects who discontinued from the study early for any other reason will be considered responders instead of missing.
- Repeat the primary analysis for the FAS, except all subjects who discontinued from the study early will be considered non-responders.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group, including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details provided in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued from the study early, and the imputed End-of-Maintenance Period ADF of partial-onset seizures will be used to determine whether a subject is a responder.
- Repeat the primary analysis for the FAS for all subjects who have at least 24 hours of interpretable recordings during both the end of Baseline Period video-EEG and the end of Maintenance Period video-EEG (rather than 48 hours). Noting that subjects who withdraw or drop out before the first 24 hours of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non-responders and will be included in the analysis; all other subjects will be missing and will not be included in this analysis.

8.1.3.3 Multiple imputation

Imputation Step

Multiple imputation using monotone regression (assuming a missing at random pattern) will be used to impute missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG. Note that the multiple imputation will be done on log-transformed ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG, using the transformation of ln (X+1), where X is the seizure ADF and ln refers to the natural log.

Multiple imputation will be performed by treatment group. All subjects eligible for the analysis will be included: observed values will be included where available and imputations only performed for missing values. The missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG in each dataset (ie, missing values for subjects who dropped out prior to completion of the End-of-Maintenance Period video-EEG but who have available data from the End-of-Baseline Period video-EEG) will be imputed using monotone regression, with a total of 100 sets of imputations being performed. Age group and center (each pooled as appropriate), and seizure ADF from the End-of-Baseline Period video-EEG (similarly

log-transformed) will be included in the imputation model. This will be done using SAS PROC MI. If the resulting multiple imputation model produces warnings or errors, then center (pooled appropriately) will not be included in the imputation model.

For the US analysis, the resulting imputed values will be used in the ANCOVA. For the EU analysis, the resulting imputed values will be back-transformed prior to being dichotomized into responder status for the logistic regression analysis.

For derivation of the EU primary efficacy variable (responder status), the log-transformed End-of-Maintenance Period seizure ADF values in the imputed datasets will be back-transformed to seizure ADF values and compared to the observed End-of-Baseline Period seizure ADF values to determine if a reduction of at least 50% in ADF of partial-onset seizures was achieved. Consequently, imputed datasets will include observed and imputed values for log-transformed seizure ADF at End-of-Maintenance (for US primary efficacy sensitivity analysis), and observed and imputed responder status at End-of-Maintenance (for EU primary efficacy sensitivity analysis).

Analysis Step – US Primary Efficacy Variable

End-of-Maintenance Period seizure ADF will be analyzed for each imputed dataset using an ANCOVA with terms for treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately), on log-transformed seizure ADF. Log-transformed Baseline seizure ADF will be used as a covariate. The results from each of the imputed datasets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE.

Analysis Step – EU Primary Efficacy Variable

The proportion of responders between LCM and placebo will be analyzed for each imputed dataset using logistic regression with treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately) as factors. The results from each of the imputed datasets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE.

8.2 Statistical analysis of the secondary efficacy variables

The analyses of the secondary efficacy variables are based on the percent and absolute change in ADF of electrographic partial-onset seizures from baseline (defined in Sections 3.2.10 and 3.2.15) and will be analyzed for the FAS unless otherwise noted; in addition, they will be analyzed for the FAS-SDV for sensitivity purposes.

8.2.1 Percent and absolute change in ADF of electrographic partial-onset seizures

A summary of the ADF of electrographic partial-onset seizures (defined in Section 3.2.10) from the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG will be presented by treatment group for the FAS and the PPS and by age group for the FAS.

The summary of the ADF of electrographic partial-onset seizures will also be presented by treatment group on all subjects who have at least 48 hours of interpretable recordings during both

the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG for the FAS, the FAS-SDV, the PPS, and for the first 244 subjects enrolled in the study for the FAS and for the FAS-SDV.

A summary of the percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG (defined in Sections 3.2.11 and 3.2.12) will be presented by treatment group for the FAS.

The summary (absolute, percent and absolute change) of the ADF of electrographic partial-onset seizures will also be presented on all subjects who have at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

8.2.2 Proportion of subjects experiencing a ≥25% to <50%, 50% to ≤75%, or >75% reduction in ADF of electrographic partial-onset seizures

The number and percentage of subjects experiencing a ≥25% to <50%, ≥50 to ≤75%, or >75% reduction in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG will be presented by treatment group. These classifications require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent reduction will be calculated as defined in Section 3.2.13.

8.2.3 Proportion of subjects experiencing no change in ADF of electrographic partial-onset seizures (between <25% reduction and <25% increase)

The number and percentage of subjects experiencing no change in ADF of partial-onset seizures (between <25% reduction and <25% increase) from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG will be presented by treatment group. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent reduction/increase will be calculated as defined in Section 3.2.13.

8.2.4 Proportion of subjects experiencing an increase in ADF of electrographic partial-onset seizures of ≥25%

The number and percentage of subjects experiencing an increase in ADF of partial-onset seizures of ≥25% from the end-of-Baseline Period video-EEG to the end-of-Maintenance Period video-EEG will be presented by treatment group. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent increase will be calculated as defined in Section 3.2.13.

8.2.5 Proportion of subjects who achieved seizure-free status

For subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG, the number and percentage of subjects who achieved "seizure-free" status from all seizure types, and from partial-onset seizure types only (defined in

Section 3.2.15) will be tabulated and presented by treatment group for the FAS, the FAS-SDV, and the PPS.

8.3 Analysis of other efficacy variable(s)

The following efficacy variables will be summarized for the FAS.

8.3.1 Clinical Global Impression of Change

The Clinical Global Impression of Change is a 7-point categorical rating scale in which the investigator assesses the subject's clinical status compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and a subject's functional status. This will be assessed at Visit 6 or at ETV in case of early termination.

The number and percentage of subjects with each Clinical Global Impression of Change value will be summarized at Visit 6 by treatment group. The denominator for the percentage calculation will be based on the number of subjects with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized at Visit 6 by treatment group. The denominator for the percentage calculation will be based on the number of subjects with non-missing values.

Clinical Global Impression of Change data will be listed.

8.3.2 Caregiver's Global Impression of Change

The Caregiver's Global Impression of Change is a 7-point categorical rating scale in which the caregiver assesses the subject's clinical status compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. This will be assessed at Visit 6 or at ETV in case of early termination.

The number and percentage of subjects by Caregiver's Global Impression of Change value will be summarized at Visit 6 by treatment group. The denominator for the percentage calculation will be based on the number of subjects with non-missing values. In addition, the 3 improvement values (Very much improved, Much improved, and Minimally improved) grouped as "Improved" and the 3 worsening values (Minimally worse, Much worse, and Very much worse) grouped as "Worsened", together with the "No change" group will be summarized at Visit 6 by treatment group. The denominator for the percentage calculation will be based on the number of subjects with non-missing values.

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

8.3.3 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. The PedsQL will be administered only in countries where a translated version is available and will be completed at Visit 3, Visit 6, and at ETV in case of early termination. The version of the PedsQL used at Visit 3 should be consistent with the subject's age at Visit 3, and should be maintained for each subject for the duration of the study. Section 3.2.16 details how the scores for the core domains are calculated.

The PedsQL completed at Visit 3 will be considered Baseline as it is expected that this will be completed prior to the first dose of study medication.

8.3.3.1 Pediatric Quality of Life Inventory (PedsQL) Ages 1-12 Months

The multidimensional PedsQL 1-12 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 5 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 1-12 months data will be listed.

8.3.3.2 Pediatric Quality of Life Inventory (PedsQL) Ages 13-24 Months

The multidimensional PedsQL 13-24 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 5 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 13-24 months data will be listed.

8.3.3.3 Pediatric Quality of Life Inventory (PedsQL) Ages 2-4 years

The multidimensional PedsQL 2-4 years generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 4 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 2-4 years data will be listed.

8.3.4 Concomitant medical procedures

Subjects who had any concomitant medical procedures during the course of the study based on the Concomitant Medical Procedures eCRF will be listed. These will be attributed to the Baseline Period and Treatment Period based on the date of the procedure. Any partial dates reported for dates of the procedures will be imputed as described in Section 4.2.5.

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

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

8.3.5 Healthcare provider consultations

Healthcare provider consultations not foreseen by the protocol will be attributed to the Baseline Period and Treatment Period based on the date of the consultation. Any partial dates reported for dates of the consultations will be imputed as described in Section 4.2.5.

The number of healthcare provider consultations per subject during the Baseline Period and during the Treatment Period will be summarized, separately, by treatment group. The number of healthcare provider consultations will also be summarized using the categories 0, 1, 2, and 3 or more.

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

All healthcare provider consultations data will be listed.

8.3.6 Hospital stays and ER visits

Hospital stays and ER visits will be attributed to the Baseline Period and Treatment Period based on admission date. Any partial dates reported for admission dates will be imputed as described in Section 4.2.5.

The number of hospital stays per subject during the Baseline Period and during the Treatment Period will be summarized, separately, by treatment group. The number of hospital stays will also be summarized using the categories 0, 1, 2, and 3 or more. The number and percentage of subjects with specific reasons for hospital stays will be summarized for the duration of the Baseline Period and for the duration of the Treatment Period, separately, by treatment group.

Duration of hospital stays (as defined in Section 3.2.17) during the Baseline Period and during the Treatment Period will be summarized, separately, by treatment group. Duration of hospital stays will also be categorized as 0 days, 1-5 days, 6-10 days, 11-15 days, and >15 days, and summarized for the duration of the Baseline Period and the duration of the Treatment Period, separately, by treatment group.

An event logged on the Hospitalization/ER Visit eCRF module where ER is marked as initial entry point will be defined as an ER visit. An ER visit with a subject transfer to an inpatient general ward will also be counted as a hospitalization. However, all other instances of ER visits (where subject transfer is not to an inpatient general ward) will not be counted as hospitalizations. Descriptive statistics for the number of ER stays for the duration of the Baseline Period and for the duration of the Treatment Period will be presented, separately, by treatment group. The number of ER visits will be tabulated using the categories 0, 1, 2, and 3 or more, and summarized by treatment group for the duration of the Baseline Period and for the duration of the Treatment Period. The number and percentage of subjects with specific reasons for ER visits

will be summarized for the duration of the Baseline Period and for the duration of the Treatment Period, separately, by treatment group.

Hospitalizations with either a partial admission or discharge date are ignored for the calculation of duration of hospital stay. However, such hospitalizations are counted for the number of hospital stays. Subjects with no hospital stays within a study period will have a duration of 0 days for that period. Should distinct records for hospital stays overlap, then the days during the overlap will only be counted once. Similarly, this also applies for ER visits.

All hospitalization and ER data will be listed.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Descriptive statistics of LCM plasma concentrations

The results of LCM plasma concentrations will be summarized using all reported decimal places and displayed to the same number of places as they are recorded in the database. Descriptive statistics will include number of subjects (n), number of subjects with plasma levels above lower limit of quantification (LOQ), arithmetic mean, SD, coefficient of variation (CV[%]), geometric mean, geometric CV(%), median, minimum, and maximum. The maximum number will be reported to 4 decimal places for any summary statistics. The CV(%) and geometric CV(%) will be presented with 1 decimal place.

Summary statistics will only be calculated if at least 2/3 of data are above the lower LOQ. Values which are less than the lower LOQ will be set to LOQ/2 for the determination of all summary statistics.

Summary tables of LCM plasma concentrations will be presented by treatment group, visit including the Last Visit, and time point for the PK-PPS. Summaries will also be performed by LCM maintenance dose level and repeated by LCM maintenance dose level and age group.

A listing of LCM plasma concentrations by age group will be presented. In addition, and as appropriate, listings of concomitant AED plasma concentrations and last intake of concomitant AEDs prior to blood sampling by age group will be presented.

9.2 Population pharmacokinetics

A population PK analysis will be performed in NONMEM. The data will be added to data from other studies; methods will be described in a DAP (Data Analysis Plan) and the results will be reported separately from SP0967.

10 SAFETY ANALYSES

All safety variables will be analyzed using descriptive methods on the SS.

10.1 Extent of exposure

The overall duration of study medication exposure (defined in Section 3.2.6) during each of the Titration Period, Maintenance Period, and Treatment Periods will be calculated, as follows:

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

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

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

The overall duration of study medication exposure will be summarized for each of the study periods defined above by treatment group, and repeated by treatment group and age group, using the levels defined in Section 3.2.7.

The median total daily dose (mg/kg/day) during the Titration Period, Maintenance Period, and Treatment Period will be summarized by treatment group, and repeated by treatment group and age group, using the levels defined in Section 3.2.7.

In addition, for the Titration Period, the number of back titration steps for each subject (categorized as: 0, 1, 2, and 3 or more), and the number of subjects with a dose change together with the number of dose changes during the interval by dose back titration occurred (categorized as: <4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day) will be summarized by treatment group, and repeated by treatment group and age group using the levels defined in Section 3.2.7.

10.2 Adverse events

Adverse events will be tabulated by MedDRA system organ class (SOC) and MedDRA preferred term (PT). The number and percentage of subjects experiencing each event at least once will be summarized. All summaries will be sorted alphabetically by SOC and by frequency of events within PTs, starting with the most frequent event overall.

Adverse events will be classified as pre-treatment, treatment-emergent, or post-treatment. Pre-treatment AEs are defined as AEs which had an onset date prior to the first dose of study medication.

Treatment-emergent AEs (TEAEs) will be defined as those events that start on or after the date of first study medication administration and within 30 days following the date of final study medication administration, or whose severity worsens within this time frame.

Post-treatment AEs are defined as AEs which had an onset date more than 30 days after the last dose of study medication.

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

An overall summary of AEs during the Treatment Period will provide the overall summary of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a serious TEAE, with a drug-related TEAE, with a severe TEAE, and with a drug-related serious TEAE. The number and percentage of subject discontinuations due to TEAEs, and the number and percentage of subjects with AEs leading to death and with TEAEs leading to death (if applicable), during the Treatment Period, will also be summarized. The overall summary of AEs during the Treatment Period will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

In addition, an overall summary of AEs during the Titration, Maintenance, Transition, Taper, and Safety Follow-Up Periods, and overall, separately, will be presented for each treatment group.

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

- Incidence of TEAEs during the Treatment Period
- Incidence of serious TEAEs during the Treatment Period
- Incidence of TEAEs leading to discontinuation of study medication during the Treatment Period

All three of these summaries will then be repeated by treatment group and age group using the levels defined in Section 3.2.7.

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

The incidence of drug-related TEAEs by seriousness (yes or no) during the Treatment Period will be presented for each treatment group by MedDRA primary SOC and PT.

The incidence of TEAEs during the Treatment Period by dose at onset (Placebo, ≥2-<4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10 -≤12mg/kg/day, and >12mg/kg/day) will be presented for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

The incidence of non-serious TEAEs occurring in more than 5% of subjects in any treatment group will be summarized for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

Other significant TEAEs during the Treatment Period, defined in Appendix 12 (Section 12.2), will be summarized for each treatment group by MedDRA primary SOC and PT. In addition, potential drug induced liver injury (PDILI) related TEAEs, defined in Appendix 12 (Section 12.3) will be presented by SOC and PT.

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

Additional subject data listings will be presented for PDILI-related TEAEs, deaths, and coronavirus-related AEs.

10.3 Clinical laboratory evaluations

Hematology and blood chemistry (including liver function tests) parameters are assessed throughout the study from Visit 1, Visit 5, Visit 6, and at ETV in case of early termination, and may also be assessed at unscheduled visits. For reporting purposes ETVs are mapped to the next scheduled visit. Laboratory parameters will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit, as appropriate.

All summaries of laboratory parameters will only summarize parameters planned based on the protocol. However, both planned and unplanned laboratory parameters will be provided in subject data listings.

Observed values of laboratory parameters and change from Baseline will be summarized by treatment group for all post-Baseline visits, and Last Visit.

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

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

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

All hematology and blood chemistry data will be listed.

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

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

10.4.1 Vital signs

Vital signs (systolic BP [SBP], diastolic BP [DBP], and pulse rate) will be assessed after at least 3 minutes at rest in a supine position throughout the study at all visits except Visit 3, at the ETV in case of early termination, and at unscheduled visits. Vital signs will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit, as appropriate.

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

Body weight will be assessed throughout the study at all visits except Visit 3, at the ETV in case of early termination, and at unscheduled visits. Body weight will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit.

Height and head circumference will be assessed at Visit 1, Visit 6, and at ETV in case of early termination. BMI will subsequently be calculated at these visits.

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

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

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

The number and percentage of subjects with a MA value, MA low value, and MA high value, at each post-Baseline visit up to Visit 6, for which SBP, DBP, pulse rate, and body weight were scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects with a value at each visit.

The abnormal vital sign criteria are defined as follows:

Table 10–1: Vital signs abnormality criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	<6m	<100 >180
	6m - <3y	<90 >150
	3y - 4y	<60 >130
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120
	3y – 4y	<80 >140
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y – 4y	<50 >80
Body Weight	1m – 4y	<3% or >97% of the normal body weight growth curve ranges[a] based on gender and the age of subject on date of weight assessment

Abbreviations: m=months, y=years. A month is defined as 28 days; a year is defined as 365.25 days.
a Source: http//www.cdc.gov/growthcharts/.

A subject data listing of all vital signs for subjects with an AE mapped to the PT bradycardia will be presented.

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

10.4.2 Electrocardiograms

Standard 12-lead ECGs (2 interpretable recordings [approximately 20 to 30 minutes apart]) will be performed at Visit 1, Visit 3, Visit 5, Visit 6, and at ETV in case of early termination. Standard 12-lead ECGs will also be performed at Visit 2 of the Transition Period, at the Taper Period, and at the Safety Follow-Up Visit, as appropriate.

Electrocardiograms will be reviewed locally and at a central ECG laboratory. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

For ECGs, Baseline will be defined as the average of all pre-dose interpretable readings for tables presenting change from Baseline of all numerical parameters (Heart rate, QTc, QTcB, PR, and QRS). For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

Observed values of ECG results will be summarized at Baseline, and for each visit and Last Visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits and Last Visit by treatment group, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, as assessed by the investigator, will be summarized at Baseline and at each post-Baseline of the Treatment Period as scheduled, and Last Visit, by treatment group. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each visit based on the worst observed outcome across all abnormalities reported at that visit. For this summary Baseline is defined as the worst assessment for ECGs taken before the first dose.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit, will also be provided by treatment group based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant. For this summary Baseline is defined as the last pre-dose ECG result. In addition, the number and percentage of subjects with a normal finding at Baseline, and an abnormal, not clinically significant finding or an abnormal, clinically significant finding, at any post-Baseline visit during the study will be presented by treatment group and overall. Subjects will be counted at most once based on the worst observed outcome across all abnormalities reported at all post-Baseline visits during the study. For this summary Baseline is defined as the last pre-dose ECG result.

A listing of ECG data will be provided for all subjects with other significant TEAEs in the Cardiac and ECG Related Terms category defined in Appendix 12 (Section 12.2). A subject data listing of all ECG parameter values for all subjects will also be presented. Listings will include results from each recording and the average of all recordings.

The number and percentage of subjects with treatment-emergent ECG abnormalities will be presented by visit and treatment group. Abnormalities reported at an unscheduled visit will be summarized under the scheduled visit preceding the unscheduled visit (if the abnormality was

not present already at the preceding scheduled visit). Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline. All ECG parameter values will be listed for subjects meeting any abnormality criteria.

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

Table 10–2: ECG abnormality criteria

Parameter	Age Range	Abnormality Criteria
QT interval (ms)	1m - 4y	≥500
QTc(F) (ms)	<6m	>490, or >15% increase from Baseline
	6m - <3y	>440, or >15% increase from Baseline
	3y – 4y	>440, or >15% increase from Baseline
QTc(B) (ms)	<6m	>490, or >15% increase from Baseline
	6m - <3y	>450, or >15% increase from Baseline
	3y – 4y	>450, or >15% increase from Baseline
PR interval (ms)	<6m	>150, or ≥25% increase from Baseline
	6m - <3y	>170, or ≥25% increase from Baseline
	3y – 4y	>180, or ≥25% increase from Baseline
QRS interval (ms)	<6m	>90, or ≥25% increase from Baseline
	6m - <3y	>90, or ≥25% increase from Baseline
	3y – 4y	>100, or ≥25% increase from Baseline
Heart rate (bpm)	<6m	<100, >180
	6m - <3y	<90, >150
	3y – 4y	<50, >120

Abbreviations: bpm=beats per minute; m=months; ms=milliseconds; QTc=corrected QT interval;

A subject data listing will be provided that identifies subjects with abnormal findings as assessed by the investigator/cardiologist after the first dose of study medication for each type of ECG abnormality.

10.4.3 Physical examination

10.4.3.1 Complete physical examination

A complete physical examination will be performed at Visit 1 and Visit 6, and at ETV in case of early termination. A complete physical examination will also be performed at Transition Visit 2 and at the Safety Follow-Up Visit, as appropriate.

The complete physical examination completed at Visit 1 will be considered Baseline.

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

Clinically significant physical examination findings subsequent to Visit 1 will be reported as AEs.

10.4.3.2 Brief physical examination

A brief physical examination will be performed at Visit 2, Visit 4, Visit 5, and Visit 6. A brief physical examination will also be performed at Transition Visit 1 and at the Taper Visit, as appropriate.

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

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

Clinically significant physical examination findings subsequent to Visit 1 will be reported as AEs.

10.4.4 Neurological examination

10.4.4.1 Complete neurological examination

A complete neurological examination will be performed at Visit 1, Visit 6, and at ETV in case of early termination. A complete neurological examination will also be performed at Transition Visit 2 and at the Safety Follow-Up Visit, as appropriate.

The complete neurological examination completed at Visit 1 will be considered Baseline.

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

For each neurological assessment, the number and percentage of subjects with a normal assessment at Baseline, and an abnormal, not clinically significant or an abnormal, clinically significant assessment at any post-Baseline visit during the study for that specific assessment will be presented by treatment group and overall. Subjects will be counted at most once based on the worst observed outcome across all abnormalities reported at all post-Baseline visits during the study for that specific assessment.

A listing of neurological examination findings from the complete neurological examination will also be provided.

Clinically significant neurological findings subsequent to Visit 1 will be reported as AEs.

10.4.4.2 Brief neurological examination

A brief neurological examination will be performed at Visit 2, Visit 4, Visit 5, and Visit 6. A brief physical examination will also be performed at Transition Visit 1 and at the Taper Visit, as appropriate.

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

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

Clinically significant neurological findings subsequent to Visit 1 will be reported as AEs.

10.4.5 Vagus nerve stimulation

Vagus nerve stimulation (VNS) status is recorded at all visits except Visit 3, at ETV in case of early termination, and at unscheduled visits, only for subjects with an implanted VNS device. Vagus nerve stimulation status will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit, as appropriate, only for subjects with an implanted device.

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

10.4.6 Achenbach Child Behavior Checklist

[redacted]

The CBCL/1½-5 comprises 100 questions with the response options of:

0=not true (as far as known)

1=somewhat of sometimes true

2=very true or often true

The CBCL/1½-5 will be grouped according to syndrome scales in Table 10–3.

[redacted]

[redacted]

If data are missing for more than 8 questions, not including question 100, then the syndrome scales will not be included in the analysis.

A Baseline assessment of the Achenbach CBCL will be performed at Visit 3; however, due to the short study duration of SP0967, the next assessment will be collected for subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.

The Baseline Achenbach CBCL assessment results will be listed for the individual subjects.

10.4.7 BRIEF-P assessment

[redacted]

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

[redacted]

The 3 subscale scores and 5 individual component scores that make up these subscale scores are outlined in Table 10–4.

[redacted]

If at least one question is missing in a subscale score, then that subscale score will be excluded from the analysis. Similarly, the GEC score and the index score containing that subscale score will also be excluded from the analysis.

A Baseline assessment of the BRIEF-P will be performed at Visit 3; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.

The Baseline BRIEF-P assessment results will be listed for the individual subjects.

10.4.8 Bayley-III Scales

[redacted]

A Baseline assessment of the Bayley-III scales will be performed; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.

The Baseline Bayley-III sum of the scaled scores entered on the eCRF module will be listed for individual subjects.

11 REFERENCES

Friede T, Kieser M. Blinded sample size recalculation for clinical trials with normal data and baseline adjusted analysis. Pharm Stat. 2011;10:8-13.

Rubin D.B. 1987. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.

12 APPENDICES

12.1 Marked abnormality criteria for laboratory data

12.1.1 Marked abnormality criteria for hematology data

Table 12–1: Hematology abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
Hematocrit	<2y	%	≤27 >45	%	≤27 >45
	2y - 4y	%	≤29 >47	%	≤29 >47
Hemoglobin	<2y	g/dL	≤9.0 >15.0	g/L	≤90 >150
	2y - 4y	g/dL	≤9.5 >16.0	g/L	≤95 >160
WBC/ Leukocytes	All	10^9/L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0
Lymphocytes Absolute	<2y	10^9/L	<1.0 >9.8	G/L	<1.0 >9.8
	2y – 4y	10^9/L	<0.7 >6.9	G/L	<0.7 >6.9
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
	<2y	10^{12}/L	<3.0	T/L	<3.0

Table 12–1: Hematology abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
RBC/ Erythrocytes	≥2y	10^{12}/L	<3.5	T/L	<3.5

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

12.1.2 Marked abnormality criteria for chemistry data

Table 12–2: Chemistry abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
AST (SGOT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
Alkaline Phosphatase	<4y	U/L	≥690	U/L	≥690
	4y		⩾834		⩾834
GGT	<6m	U/L	≥522	U/L	≥522
	6m - <1y	U/L	≥279	U/L	≥279
	1y - 4y	U/L	≥66	U/L	≥66
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	2m-<1y	g/dL	<3.0 >11.9	g/L	<30 >119
	1y - 4y	g/dL	<4.3 >12.0	g/L	<43 >120
Albumin	<1y	g/dL	<1.6 >7.2	g/L	<16 >72
	≥1y - 4y	g/dL	<2.4 >8.4	g/L	<24 >84
BUN	<1y	mg/dL	≥24	mmol/L	≥8.568
	1y - 4y	mg/dL	≥36	mmol/L	≥12.852
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y	mg/dL	>60	mmol/L	>10.02
Creatinine	1y - 4y	mg/dL	>1.2	umol/L	>106.8
Creatinine Clearance[a b]	All	mL/min	<50	mL/s	<0.835

Table 12–2: Chemistry abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
Bicarbonate	>1m - 4y	mEq/L	<15 >38	mmol/L	<15 >38
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - 4y	mg/dL	<7.4 >11.7	mmol/L	<1.85 >2.925
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	1y - 4y	mg/dL	<1.8 >7.4	mmol/L	<0.5814 >2.3902
Potassium	<1y	mEq/L	≤3.0 ≥6.5	mmol/L	≤3.0 ≥6.5
	≥1y	mEq/L	≤3.0 ≥6.0	mmol/L	≤3.0 ≥6.0
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151
Glucose	>1m - 4y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99
Total Cholesterol	≥1y	mg/dL	>250	mmol/L	>6.475
LDL (calculated)	1y – 4y	mg/dL	>140	mmol/L	>3.626
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y	mg/dL	<20	mmol/L	<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y	mg/dL	>300	mmol/L	>3.39
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996
	1y - 4y	mg/dL	>6.5	umol/L	>386.62

Table 12–2: Chemistry abnormality criteria

Parameter	Age Range	Unit (conventional)	Abnormality criteria (conventional unit)	Unit (standard)	Abnormality criteria (standard unit)
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y	ug/dL	≤3.8 ≥13.5	nmol/L	≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >4.5	g/L	<10 >45
	≥1y	g/dL	<1.2 >5.3	g/L	<12 >53

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

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

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

12.2 Other Significant TEAEs

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

MedDRA Preferred Term
Ventricular tachyarrhythmia
Implantable defibrillator insertion
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation
Suicide attempt
Intentional self-injury
Self-injurious behaviour
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder
Decreased appetite
Diet refusal
Hypophagia
Food aversion
Abnormal behaviour

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

MedDRA Preferred Term for PDILI
Acute hepatic failure
Alanine aminotransferase increased
Allergic hepatitis
Aspartate aminotransferase increased
Asterixis
Blood bilirubin abnormal
Blood bilirubin increased
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Chronic hepatitis
Coma hepatic
Cryptogenic cirrhosis
Drug-induced liver injury
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic failure
Hepatic infiltration eosinophilic
Hepatic necrosis
Hepatic steatosis
Hepatitis
Hepatitis acute

MedDRA Preferred Term for PDILI
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatotoxicity
Hyperbilirubinaemia
Icterus index increased
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Liver disorder
Liver injury
Mixed liver injury
Non-alcoholic steatohepatitis
Ocular icterus
Subacute hepatic failure

13 AMENDMENTS TO THE STATISTICAL ANALYSIS PLAN

13.1 Amendment 1

This amendment was done to reflect the changes in Protocol Amendment #3. The primary change is to the source of seizure data from the central reader's interpretation of EEG to the investigator's (local) EEG for analyses. Additional changes include the expanded details on the multiple imputation methodology, clarifications on the analyses of seizure data and the handling of age groups in several analyses, an update to the List of Other Significant AEs, the inclusion of a list of AEs for PDILI, as well as some style changes.

Change #1

SAP/Amendment Number and Date

Final SAP 07 Oct 2017

Was changed to:

Final SAP	07 Oct 2017
Amendment #1	05 Feb 2019

Change #2

List of abbreviations

Added abbreviation for PDILI

Change #3

Section 2.2.1.2

- Proportion of subject who achieved "seizure-free" status (yes/no) for subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG.

Was changed to:

- Proportion of subjects who achieved "seizure-free" status (yes/no) from all seizures, and from partial-onset seizure types only for subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG.

Change #4

Section 2.3

Subjects will be enrolled in the following age categories as detailed below:

- ≥1 month to <6 months of age (≥25 subjects)
- ≥6 months to <1 year of age (≥25 subjects)
- ≥1 year to <2 years of age (≥25 subjects)
- ≥2 years to <4 years of age (≥20 subjects)

Was changed to:

Every attempt will be made to enroll subjects in the following age categories as detailed below:

- ≥1 month to <6 months of age (≥25 subjects)
- ≥6 months to <1 year of age (≥25 subjects)
- ≥1 year to <2 years of age (≥25 subjects)
- ≥2 years to <4 years of age (≥20 subjects)

Change #5

Section 2.4 Sample size

Subjects are randomized into the study based on the investigator's interpretation of the video-EEG to meet study entry requirements; however, there may be a difference of interpretation of the number of seizures counted on the End-of-Baseline Period video-EEG between the central reader and the investigator. To account for an anticipated difference of interpretation of the End of-Baseline Period video-EEG of 5% as well as the potential subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.

Was changed to:

Subjects are randomized into the study based on the initial interpretation of the video-EEG to meet study entry requirements. However, the subsequent detailed assessment of seizure types and counts needed for the efficacy analyses could lead to a discrepancy in seizure counts (ie, a subject initially thought to be eligible is later found to have fewer than the required number of partial-onset seizures during the End-of-Baseline Period video-EEG).To account for an anticipated difference of interpretation of the End-of-Baseline Period video-EEG of 5% as well as the potential subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.

Change #6

Section 3.2.9

Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.

The video-EEG recordings will be evaluated locally by the investigator, sub investigator, or qualified designated reader. Subjects who discontinue on or before Day 20 will not require an End-of-Maintenance Period video-EEG.

<u>Infants aged ≥1 month to ≤6 months</u>

Partial-onset seizure frequency for infants aged ≥1 month to ≤6 months will be based on electrographic seizures.

The total number of partial-onset seizures is calculated as the total number of type IA/IB electrographic seizures plus the total number of type IA/IB electroclinical seizures plus the total number of type IC seizures.

The total number of seizures is calculated as the total number of partial-onset seizures (as defined above) plus the total number of other seizure types reported.

Infants aged >6 months to <4 years

Partial-onset seizure frequency for infants aged >6 months to <4 years will be based on electrographic seizures with an accompanying clinical correlate.

The total number of partial-onset seizures is calculated as the total number of type IA/IB electroclinical seizures plus the total number of type IC seizures.

The total number of seizures is calculated as the total number of partial onset seizures (as defined above) plus the total number of other seizure types reported.

For the purposes of this SAP, the term electrographic partial-onset seizures will be used to define electrographic partial-onset seizures with or without clinical correlate; electrographic and electroclinical partial-onset seizures will be included for subjects aged ≥1 month to ≤6 months, and electroclinical partial-onset seizures will be included for subjects aged >6 months to <4 years.

Calculation of the End-of-Baseline Period ADF of electrographic partial-onset seizures will be based on the results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) at Visits 2 and 3. The End-of-Maintenance Period ADF of electrographic partial-onset seizures will be based on results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) at Visit 6.

Was changed to:

Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.

The video-EEG recordings will be evaluated locally by the investigator, sub investigator, or qualified designated reader. Subjects who discontinue on or before Day 20 will not require an End-of-Maintenance Period video-EEG.

For the purposes of this SAP, the term electrographic partial-onset seizures will be used to define electrographic partial-onset seizures with or without clinical correlate; electrographic and electroclinical partial-onset seizures will be included for subjects aged ≥1 month to ≤6 months, and electroclinical partial-onset seizures will be included for subjects aged >6 months to <4 years.

Infants aged ≥1 month to ≤6 months

Partial-onset seizure frequency for infants aged ≥1 month to ≤6 months will be based on electrographic seizures.

The total number of partial-onset seizures is calculated as the total number of type IA/IB electrographic seizures plus the total number of type IA/IB electroclinical seizures plus the total number of type IC seizures.

The total number of seizures is calculated as the total number of partial-onset seizures (as defined above) plus the total number of other seizure types reported.

Infants aged >6 months to <4 years

Partial-onset seizure frequency for infants aged >6 months to <4 years will be based on electrographic seizures with an accompanying clinical correlate.

The total number of partial-onset seizures is calculated as the total number of type IA/IB electroclinical seizures plus the total number of type IC seizures.

The total number of seizures is calculated as the total number of partial onset seizures (as defined above) plus the total number of other seizure types reported.

Calculation of the End-of-Baseline Period ADF of electrographic partial-onset seizures will be based on the results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) at Visits 2 and 3. The End-of-Maintenance Period ADF of electrographic partial-onset seizures will be based on results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) at Visit 6.

Change #7

3.2.15 Seizure free status

At least 48 hours of interpretable recordings during the End-of-Maintenance Period video-EEG is required to determine a subject's seizure-free status.

All seizures

A subject is considered seizure free from all seizures if the End-of-Maintenance Period video-EEG has 0 (zero) seizures reported, that is, from all seizure types not just partial-onset seizure types.

Partial-onset seizures

A subject is considered seizure free from partial-onset seizures if the End-of-Maintenance Period video-EEG has 0 (zero) partial-onset seizures reported.

Was changed to:

At least 48 hours of interpretable recordings during the End-of-Maintenance Period video-EEG is required to determine a subject's seizure-free status. As above, the term electrographic partial-onset seizures will be used to define electrographic partial-onset seizures with or without clinical correlate; electrographic and electroclinical partial-onset seizures will be included for subjects aged ≥1 month to ≤6 months, and electroclinical partial-onset seizures will be included for subjects aged >6 months to <4 years

All seizures

A subject is considered seizure free from all seizures if the End-of-Maintenance Period video-EEG has 0 (zero) seizures reported, that is, from all seizure types not just partial-onset seizure types.

Partial-onset seizures

A subject is considered seizure free from partial-onset seizures if the End-of-Maintenance Period video-EEG has 0 (zero) partial-onset seizures reported.

Change #8

3.9 Changes to protocol-defined analyses

Further clarification of the definition of seizure-free status has been included. Seizure free from all seizure types and seizure free from partial-onset seizures, only, will be analyzed separately.

For one of the additional sensitivity analyses on the primary efficacy variable, multiple imputation using Monotone regression will be used.

Was changed to:

For sensitivity analyses requiring multiple imputation, missing data multiple imputation will not be performed by treatment group and age group (≥ 1 month to < 6 months of age, ≥ 6 months to < 1 year of age, ≥ 1 year to < 2 years of age, and ≥ 2 years to < 4 years of age). Multiple imputation will instead be performed by treatment group (adjusting for age group.

For analyses of LCM plasma concentrations, in addition to summarizing descriptive statistics as described in the protocol, all tabulations will be performed by LCM maintenance dose level and separately by LCM maintenance dose level and age group.

Change #9

Section 4.1

The primary efficacy analysis and planned sensitivity analyses will be adjusted for log-transformed Baseline seizure ADF and center (appropriately pooled) in the analysis of covariance (ANCOVA) models. Other statistical models may be adjusted for covariates, and any such adjustments will be described in the context of the analyses performed.

Was changed to:

The primary efficacy analysis and planned sensitivity analyses will be adjusted for log-transformed Baseline seizure ADF, age category (4 age stratification categories, pooled as appropriate) and center (appropriately pooled) in the analysis of covariance (ANCOVA) models. Other statistical models may be adjusted for covariates, and any such adjustments will be described in the context of the analyses performed.

Change #10

Section 4.2.5

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of AEs
- Start and stop dates of concomitant medication
- Start and stop dates of study medication

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

Was changed to:

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of AEs
- Start and stop dates of concomitant medication
- Start and stop dates of study medication

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

For calculation of date of diagnosis and duration of diagnosis the following rules will be used for imputation of incomplete dates:

If the month and year are available, the diagnosis date is imputed as the later of the following dates: the first day of the month, the subject's birthdate, or the date of the first seizure (if available). If only a year is available, the later of the following dates will be imputed: January 1st of the year, the subject's birthdate, and the date of the first seizure.

Change #11

Section 4.8 Examination of subgroups

Age groups as defined in Section 3.2.7 will be used within summaries of disposition, demography, exposure and adverse events.

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

Was changed to:

Age groups as defined in Section 3.2.7 will be used within summaries of disposition, demography, exposure and adverse events.

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

Descriptive summaries of US and EU primary efficacy endpoints will be provided by age group and treatment group.

Change #12

Section 5.1 Subject disposition

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

Was changed to:

The number of subjects screened, and the number and percentage of those subjects who were screen failures, broken down by primary reason for screening failure will be presented by age group and overall. Screen failures are allowed to be re-screened after consultation with the

medical monitor. Subjects who are re-screened and subsequently enrolled and randomized are not included in screen failure counts. These subjects will be provided in a listing with previous subject ID and date of re-screening.

Change #13

Section 6.4.5 Concomitant AEDs

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

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

Was Changed to:

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

Concomitant AEDs will be defined by a manual review of all unique combinations of ATC codes and indications reported in the database to identify medications taken to treat epilepsy.

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

Change #14

Section 8.1.2.1 Primary analysis of the primary efficacy variable for the US

Seizure ADF will be analyzed using an ANCOVA with terms for treatment and center (pooled appropriately), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF and ln refers to the natural log. Log-transformed Baseline seizure ADF will be used as a covariate.

Was changed to:

Seizure ADF will be analyzed using an ANCOVA with terms for treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF and ln refers to the natural log. Log-transformed Baseline seizure ADF will be used as a covariate.

Change #15

Section 8.1.2.1 Primary analysis of the primary efficacy variable for the US

Assumptions for the parametric model described above will be evaluated by diagnostic (e.g., Shapiro-Wilk test for normality) and graphical methods such as residual plots, including normal probability plots, histograms, and plots of residuals versus Baseline covariate values and treatment. An assessment will be made with regards to the influence of individual observations (e.g., extreme outliers) on the analysis. To the extent feasible, such potential influential observations will be identified prior to unblinding, and an assessment will be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If deemed that a non-parametric method is

warranted, an ANCOVA model on rank of seizure ADF with terms for treatment and center (pooled appropriately) will be employed for the primary analysis. Ranked Baseline seizure ADF will be used as a covariate.

Was changed to:

Assumptions for the parametric model described above will be evaluated by diagnostic (eg, Shapiro-Wilk test for normality) and graphical methods such as residual plots, including normal probability plots, histograms, and plots of residuals versus Baseline covariate values and treatment. An assessment will be made with regards to the influence of individual observations (eg, extreme outliers) on the analysis. To the extent feasible, such potential influential observations will be identified prior to unblinding, and an assessment will be made with regard to the potential impact of such data, including the evaluation of alternative statistical methodology such as non-parametric methods. If deemed that a non-parametric method is warranted, an ANCOVA model on rank of seizure ADF with terms for age group, treatment, and center (pooled appropriately) will be employed for the primary analysis. Ranked Baseline seizure ADF will be used as a covariate.

Change #16

Section 8.1.2.2 Primary analysis of the primary efficacy variable for the EU

The proportion of responders between LCM and placebo will be analyzed using logistic regression with treatment and center (pooled appropriately) as factors. From this model, odds ratios will be presented along with the corresponding 95% CI and p-value. In addition, the number and percentage of subjects with a 50% or more reduction in seizure ADF will be presented.

Was changed to:

The proportion of responders between LCM and placebo will be analyzed using logistic regression with treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately) as factors. From this model, odds ratios will be presented along with the corresponding 95% CI and p-value. In addition, the number and percentage of subjects with a 50% or more reduction in seizure ADF will be presented by treatment group and age group.

Change #17

Section 8.1.3 Sensitivity analyses of the primary efficacy variables

Was changed to:

For sensitivity analyses that are applied to subjects who discontinued early, the population will include all subjects with at least 48 interpretable hours of EEG data at both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, and additionally all subjects with at least 48 interpretable hours of End-of-Baseline Period video-EEG and missing status for End-of-Maintenance Period video-EEG as a consequence of early discontinuation.

Change #18

Section 8.1.3.1 Sensitivity analyses of the primary efficacy variable for the US

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise stated:

Was changed to:

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

Change #19

Section 8.1.3.1 Sensitivity analyses of the primary efficacy variable for the US

- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using Monotone regression assuming a log-normal distribution. This will be applied for all subjects who discontinued early from the study.

Was changed to:

- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued early from the study.

Change #20

Section 8.1.3.2 Sensitivity analyses of the primary efficacy variable for the EU

- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using Monotone regression assuming a log-normal distribution. This will be applied for all subjects who discontinued early from the study.

Was changed to:

- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details in Section 8.1.3.2.1) using Monotone regression. This will be

applied for all subjects who discontinued early from the study, and the imputed End-of-Maintenance Period ADF of partial onset seizures will be used to determine whether a subject is a responder.

Change #21

Section 8.1.3.3 Multiple Imputation

Multiple Imputation using Monotone regression (assuming a missing at random pattern) will be used to impute missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG. One hundred (100) imputed datasets will be created before combining them into a single inference. Note that the multiple imputation will be done on the continuous ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG. For the EU analysis, this variable will be dichotomized for the logistic regression analysis.

Was changed to:

Imputation Step

Multiple imputation using monotone regression (assuming a missing at random pattern) will be used to impute missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG. Note that the multiple imputation will be done on log-transformed ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG, using the transformation of ln (X+1), where X is the seizure ADF and ln refers to the natural log.

Multiple imputation will be performed by treatment group. All subjects eligible for the analysis will be included: observed values will be included where available and imputed values from multiple imputation will be included for subjects needing such imputed values because of missing values. The missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG in each dataset (ie, missing values for subjects who dropped out prior to completion of the End-of-Maintenance Period video-EEG but who have available data from the End-of-Baseline Period video-EEG) will be imputed using monotone regression, with a total of 100 sets of imputations being performed. Age group and center (each pooled as appropriate), and seizure ADF from the End-of-Baseline Period video-EEG (similarly log-transformed) will be included in the imputation model. If the resulting multiple imputation model produces warnings or errors, then center (pooled appropriately) will not be included in the imputation model.

For the US analysis, the resulting imputed values will be used in the ANCOVA. For the EU analysis, the resulting imputed values will be back-transformed prior to being dichotomized into responder status for the logistic regression analysis.

For derivation of the EU primary efficacy variable (responder status), the log-transformed End-of-Maintenance Period seizure ADF values in the imputed datasets will be back-transformed to seizure ADF values and compared to the observed End-of-Baseline Period seizure ADF values to determine if a reduction of at least 50% in ADF of partial-onset seizures was achieved. Consequently, imputed datasets will include observed and imputed values for log-transformed seizure ADF at End-of-Maintenance (for US primary efficacy sensitivity analysis), and observed and imputed responder status at End-of-Maintenance (for EU primary efficacy sensitivity analysis).

Analysis Step – US Primary Efficacy Variable

End-of-Maintenance Period seizure ADF will be analyzed for each imputed dataset using an ANCOVA with terms for treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately), on log-transformed seizure ADF. Log-transformed Baseline seizure ADF will be used as a covariate. The results from each of the imputed datasets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE.

Analysis Step – EU Primary Efficacy Variable

The proportion of responders between LCM and placebo will be analyzed for each imputed dataset using logistic regression with treatment, age category (4 age stratification categories, pooled as appropriate) and center (pooled appropriately) as factors. The results from each of the imputed datasets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE.

Change #22

Section 8.2 Statistical analysis of the secondary efficacy variables

The analyses of the secondary efficacy variables are based on the percent and absolute change in ADF of electrographic partial-onset seizures from baseline (defined in Sections 3.2.10 to 3.2.15).

Percent and absolute change in ADF of electrographic partial-onset seizures

A summary of the ADF of electrographic partial-onset seizures (defined in Section 3.2.10) from the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG will be presented by treatment group. A summary of the percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG (defined in Sections 3.2.11 and 3.2.12) will be presented by treatment group.

8.2.1 Proportion of subjects experiencing a ≥25% to <50%, 50% to ≤75%, or >75% reduction in ADF of electrographic partial-onset seizures

The number and percentage of subjects experiencing a ≥25% to <50%, ≥50 to ≤75%, or >75% reduction in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG will be presented by treatment group. These classifications require at least 48 hours of interpretable recordings during both the End-of- Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent reduction will be calculated as defined in Section.

8.2.2 Proportion of subjects experiencing no change in ADF of electrographic partial-onset seizures (between <25% reduction and <25% increase)

The number and percentage of subjects experiencing no change in ADF of partial-onset seizures (between <25% reduction and <25% increase) from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG will be presented by treatment group. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG. Percent reduction/increase will be calculated as defined in Section.

8.2.3 Proportion of subjects experiencing an increase in ADF of electrographic partial-onset seizures of ≥25%

The number and percentage of subjects experiencing an increase in ADF of partial-onset seizures of ≥25% from the end-of-Baseline Period video-EEG to the end-of-Maintenance Period video-EEG will be presented by treatment group. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent increase will be calculated as defined in Section.

8.2.4 Proportion of subjects who achieved seizure-free status

For subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG, the number and percentage of subjects who achieved "seizure-free" status from all seizure types, and from partial-onset seizure types only (defined in Section 3.2.15) will be tabulated and presented by treatment group for both the FAS and the PPS.

Was changed to:

The analyses of the secondary efficacy variables are based on the percent and absolute change in ADF of electrographic partial-onset seizures from baseline (defined in Sections 3.2.10 and 3.2.15).

8.2.1 Percent and absolute change in ADF of electrographic partial-onset seizures

A summary of the ADF of electrographic partial-onset seizures (defined in Section 3.2.10) from the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG will be presented by treatment group and by age group.

A summary of the percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG (defined in Sections 3.2.11 and 3.2.12) will be presented by treatment group.

8.2.2 Proportion of subjects experiencing a ≥25% to <50%, 50% to ≤75%, or >75% reduction in ADF of electrographic partial-onset seizures

The number and percentage of subjects experiencing a ≥25% to <50%, ≥50 to ≤75%, or >75% reduction in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG will be presented by treatment group. These classifications require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent reduction will be calculated as defined in Section 3.2.13.

8.2.3 Proportion of subjects experiencing no change in ADF of electrographic partial-onset seizures (between <25% reduction and <25% increase)

The number and percentage of subjects experiencing no change in ADF of partial-onset seizures (between <25% reduction and <25% increase) from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG will be presented by treatment group. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent reduction/increase will be calculated as defined in Section 3.2.13.

8.2.4 Proportion of subjects experiencing an increase in ADF of electrographic partial-onset seizures of ≥25%

The number and percentage of subjects experiencing an increase in ADF of partial-onset seizures of ≥25% from the end-of-Baseline Period video-EEG to the end-of-Maintenance Period video-EEG will be presented by treatment group. This classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Percent increase will be calculated as defined in Section 3.2.13.

8.2.5 Proportion of subjects who achieved seizure-free status

For subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG, the number and percentage of subjects who achieved "seizure-free" status from all seizure types, and from partial-onset seizure types only (defined in Section 3.2.15) will be tabulated and presented by treatment group for both the FAS and the PPS.

Change #23

Section 9.1 Descriptive statistics of LCM plasma concentrations

The results of LCM plasma concentrations will be summarized using all reported decimal places and displayed to the same number of places as they are recorded in the database. Descriptive statistics will include number of subjects (n), number of subjects with plasma levels above lower limit of quantification (LOQ), arithmetic mean, SD, coefficient of variation (CV[%]), geometric mean, geometric CV(%), median, minimum, and maximum. The maximum number will be reported to 4 decimal places for any summary statistics. The CV(%) and geometric CV(%) will be presented with 1 decimal place.

Summary statistics will only be calculated if at least 2/3 of data are above the lower LOQ. Values which are less than the lower LOQ will be set to LOQ/2 for the determination of all summary statistics.

Summary tables of LCM plasma concentrations will be presented by treatment group, visit and Last Visit for the PK-PPS.

A listing of LCM plasma concentrations by age group will be presented. In addition, and as appropriate, listings of concomitant AED plasma concentrations and last intake of concomitant AEDs prior to blood sampling by age group will be presented.

Was changed to:

The results of LCM plasma concentrations will be summarized using all reported decimal places and displayed to the same number of places as they are recorded in the database. Descriptive statistics will include number of subjects (n), number of subjects with plasma levels above lower limit of quantification (LOQ), arithmetic mean, SD, coefficient of variation (CV[%]), geometric mean, geometric CV(%), median, minimum, and maximum. The maximum number will be reported to 4 decimal places for any summary statistics. The CV(%) and geometric CV(%) will be presented with 1 decimal place.

Summary statistics will only be calculated if at least 2/3 of data are above the lower LOQ. Values which are less than the lower LOQ will be set to LOQ/2 for the determination of all summary statistics.

Summary tables of LCM plasma concentrations will be presented by treatment group, visit and Last Visit for the PK-PPS. Summaries will also be performed by LCM maintenance dose level, and repeated by LCM maintenance dose level and age group.

A listing of LCM plasma concentrations by age group will be presented. In addition, and as appropriate, listings of concomitant AED plasma concentrations and last intake of concomitant AEDs prior to blood sampling by age group will be presented.

Change #24

Section 10.1 Extent of exposure

In addition, for the Titration Period, the number of back titration steps for each subject (categorized as: 0, 1, 2, and 3 or more), the number of subjects with a dose change together with the number of dose changes during the interval by dose back titration occurred (categorized as: <4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day), the number of up titration steps for each subject (categorized as: 0, 1-3, 4-5, and ≥6), and the number of subjects with a dose change together with the number of dose changes during the interval by dose up titration occurred (categorized as: <4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day), will be summarized by treatment group, and repeated by treatment group and age group using the levels defined in Section 3.2.7.

Was Changed to:

In addition, for the Titration Period, the number of back titration steps for each subject (categorized as: 0, 1, 2, and 3 or more), and the number of subjects with a dose change together with the number of dose changes during the interval by dose back titration occurred (categorized as: <4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day), will be summarized by treatment group, and repeated by treatment group and age group using the levels defined in Section 3.2.7.

Change #25

Section 10.2 Adverse Events

The incidence of TEAEs during the Treatment Period by dose at onset (Placebo, >0-<2mg/kg/day, ≥2-<4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day) will be presented for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

The incidence of non-serious TEAEs occurring in more than 5% of subjects in any treatment group will be summarized for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

Other significant TEAEs during the Treatment Period, defined in Appendix 12 (Section 12.2), will be summarized for each treatment group by MedDRA primary SOC and PT.

Was changed to:

The incidence of TEAEs during the Treatment Period by dose at onset (Placebo, ≥2-<4mg/kg/day, ≥4-<6mg/kg/day, ≥6-<8mg/kg/day, ≥8-<10mg/kg/day, ≥10-≤12mg/kg/day, and >12mg/kg/day) will be presented for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

The incidence of non-serious TEAEs occurring in more than 5% of subjects in any treatment group will be summarized for each treatment group by MedDRA primary SOC and PT, and will be repeated by treatment group and age group using the levels defined in Section 3.2.7.

Other significant TEAEs during the Treatment Period, defined in Appendix 12 (Section 12.2), will be summarized for each treatment group by MedDRA primary SOC and PT. In addition potential drug induced liver injury (PDILI) related TEAEs, defined in Appendix 12 (Section 12.3) will be presented by SOC and PT.

Change #26

Section 10.3 Clinical Laboratory evaluations

Hematology and blood chemistry (including liver function tests) parameters are assessed throughout the study from Visit 1, Visit 5, Visit 6, and at ETV in case of early termination, and may also be assessed at unscheduled visits. Laboratory parameters will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit, as appropriate.

Was changed to:

Hematology and blood chemistry (including liver function tests) parameters are assessed throughout the study from Visit 1, Visit 5, Visit 6, and at ETV in case of early termination, and may also be assessed at unscheduled visits. For reporting purposes ETVs are mapped to the next scheduled visit. Laboratory parameters will also be assessed during the Transition Period, Taper Period, and at the Safety Follow-Up Visit, as appropriate.

Change #27

Section 10.4.2 Electrocardiograms

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, as assessed by the investigator, will be summarized at Baseline and at each post-Baseline of the Treatment Period as scheduled, and Last Visit, by treatment group. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each visit based on the worst observed outcome across all abnormalities reported at that visit.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit, will also be provided by treatment group based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant. In addition, the number and percentage of subjects with a normal finding at Baseline, and an abnormal, not clinically significant finding or an abnormal, clinically significant finding, at any post-Baseline visit during the study will be presented by treatment group and overall. Subjects will be counted at most once based on the worst observed outcome across all abnormalities reported at all post-Baseline visits during the study.

Was changed to:

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding, as assessed by the investigator, will be summarized at Baseline and at each post-Baseline of the Treatment Period as scheduled, and Last Visit, by treatment group. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Subjects are counted at most once at each visit based on the worst observed outcome across all abnormalities reported at that visit. For this summary Baseline is defined as the worst assessment for ECGs taken before the first dose.

Summaries of shifts from Baseline to post-Baseline visits, and from Baseline to Last Visit, will also be provided by treatment group based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant. For this summary Baseline is defined as the last pre-dose ECG result. In addition, the number and percentage of subjects with a normal finding at Baseline, and an abnormal, not clinically significant finding or an abnormal, clinically significant finding, at any post-Baseline visit during the study will be presented by treatment group and overall. Subjects will be counted at most once based on the worst observed outcome across all abnormalities reported at all post-Baseline visits during the study. For this summary Baseline is defined as the last pre-dose ECG result.

Change #28

References

Friede T, Kieser M. Blinded sample size recalculation for clinical trials with normal data and baseline adjusted analysis. Pharm Stat. 2011;10:8-13.

Was changed to:

Friede T, Kieser M. Blinded sample size recalculation for clinical trials with normal data and baseline adjusted analysis. Pharm Stat. 2011;10:8-13.

Rubin D.B. 1987. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.

Change # 29

Appendix 12 Table 12-2 Chemistry abnormality criteria

A row was added to table 12-2 Chemistry abnormality data to include a criteria for Alkaline Phosphatase for age 4y. The row:

Alkaline Phosphatase	<4y	U/L	≥690	U/L	≥690

Was changed to:

	<4y		≥690	U/L	≥690

Alkaline Phosphatase	4y	U/L	≥834		≥834

Change #30

12.2 Other significant TEAEs

MedDRA Preferred Term
Hepatotoxicity related terms
Hepatitis toxic
Hepatotoxicity
Cardiac and ECG Related Terms
Atrioventricular block complete
Atrioventricular block second degree
Bradyarrhythmia
Bradycardia
Cardiac pacemaker insertion
Atrial fibrillation
Atrial flutter
Sinus bradycardia
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased
Sick sinus syndrome
Suicidality related terms
Completed suicide
Depression suicidal
Suicidal behaviour

MedDRA Preferred Term
Suicidal ideation
Suicide attempt
Intentional self-injury
Self injurious behaviour
Self-injurious ideation
Intentional overdose
Poisoning deliberate
Additional terms
Loss of consciousness
Syncope

Was changed to:

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

MedDRA Preferred Term
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased
Sick sinus syndrome
Atrial conduction time prolongation
Atrioventricular dissociation
Conduction disorder
Cardiac fibrillation
Cardiac flutter
Sinus arrest
Torsade de pointes
Ventricular asystole
Ventricular flutter
Ventricular tachyarrhythmia
Implantable defibrillator insertion
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation
Suicide attempt
Intentional self-injury
Self-injurious behaviour

MedDRA Preferred Term
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder
Decreased appetite
Diet refusal
Hypophagia
Food aversion
Abnormal behaviour

Change #31

Section 12.3 was added:

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

MedDRA Preferred Term for PDILI
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Drug-induced liver injury
Hepatitis cholestatic
Hyperbilirubinaemia

MedDRA Preferred Term for PDILI
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

MedDRA Preferred Term for PDILI
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

13.2 Amendment 2

The primary purpose of this amendment is to include additional analyses to address the impact of the global pandemic of COVID-19. Due to the global pandemic of COVID-19, standard data cleaning and reconciliation processes have changed for some sites. In particular, monitors may be unable to perform their standard on-site visits with 100% source data verification of all eCRF pages. For video-EEG data, remote monitoring will instead be performed in which edit checks will be utilized to confirm correct data entry. Additional sensitivity analyses to address the COVID-19 impacts on efficacy results have been added, including repeating analyses of the primary and secondary efficacy variables which exclude subjects whose data cleaning and reconciliation was performed using these new processes. Further, the scoring details of the PedsQL for subjects ≤24 months of age was updated to make it consistent with other SAPs and protocols in the LCM pediatric program. Other editorial and clarification updates have also been made.

Change #1

SAP/Amendment Number and Date

Final SAP	07 Oct 2017
Amendment #1	05 Feb 2019

Was changed to:

Final SAP	07 Oct 2017
Amendment #1	05 Feb 2019
Amendment #2	07 May 2020

Change #2

List of Abbreviations

Added abbreviations for FAS-SDV and MI.

Change #3

3.2.16 Pediatric Quality of Life Inventory (PedsQL)

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

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

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

Was changed to:

The PedsQL is a validated instrument that consist of generic core scales suitable for use of pediatric population, including those with acute or chronic health conditions. The PedsQL Measurement Model consists of developmentally appropriate forms of pediatric subjects ≥1 month to ≤12 months, ≥13 month to ≤24 months, and >2 years to ≤4 years of age. For each subject, the same version of the PedsQL used at Visit 3 (Baseline) should be maintained for the duration of the study.

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

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

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

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

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

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

The above algorithm will also be used to calculate an overall total scale score (all scales), the psychosocial health summary score (a combination of the emotional, social, and cognitive functioning questions), and the physical health summary score (a combination of the physical functioning and physical symptoms questions) for each subject ≤24 months of age, and an overall total scale score (all scales), the psychosocial health summary score (a combination of the emotional, social and school functioning questions), and the physical health summary score (the physical functioning questions) for each subject >2 years age.

Change #4

Section 3.4 Protocol deviations

The following text has been added in this section:

In addition, protocol deviations related to the impact of the global pandemic of novel coronavirus (COVID-19) will be identified, reviewed, and agreed upon prior to unblinding of the database.

Change #5

Section 3.5 Analysis Sets

Addition of new analysis set FAS-SDV (Section 3.5.3), which will include all subjects in the FAS population who have both their End-of-Baseline Period and End-of-Maintenance Period video-EEG eCRF pages source data verified using on-site monitoring processes.

Subsequent sections were consequently renumbered.

Change #6

Addition of a new Section 3.8 (which renumbered subsequent sections) titled “Age strata pooling strategy”.

Change #7

Section 4.6 Use of an efficacy subset of subjects

The FAS, defined in Section 3.5.2, is the primary analysis set for the efficacy analyses.

The PPS is the secondary analysis set for the efficacy analyses. No additional efficacy subsets are defined for this study.

Was changed to:

The FAS, defined in Section 3.5.2, is the primary analysis set for the efficacy analyses.

The primary and secondary efficacy analysis will be repeated on the FAS-SDV, defined in Section 3.5.3.

The primary analyses will be repeated on the first 244 subjects enrolled in the study for the FAS and FAS-SDV. The first 244 subjects enrolled in the study will be determined using the date of informed consent. In case of ties, date of randomization will be used.

The PPS is the secondary analysis set for the efficacy analyses.

Change #8

In Section 5.1 Subject disposition, the additional analysis set FAS-SDV is included.

Change #9

Section 5.2 Protocol deviations

The following text has been added in this section:

An additional listing of protocol deviations related to the impact of the global pandemic of novel coronavirus (COVID-19) will be provided.

Change #10

Section 6.1 Demographics

The following additional demographic variables have been added in this section:

- Region (North America, Latin America, Western Europe, Eastern Europe, Asia/Pacific/Other)
- Country (Argentina, Brazil, China, Croatia, Czech Republic, France, Georgia, Greece, Hungary, Israel, Italy, Lithuania, Mexico, Philippines, Poland, Portugal, Republic of Moldova, Republic of Korea/South Korea, Romania, Russia, Serbia, Taiwan, Thailand, Ukraine, US)
- Center Pool (as determined at the final DEM prior to unblinding the study)

Change #11

Section 7 Measurements of Treatment Compliance

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

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

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

Where:

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

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

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

Where:

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

Baseline weight is the most recent IVRS weight reported before a subject is dosed.

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

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

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

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

Was changed to:

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

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

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

Where:

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

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

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

Where:

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

Baseline weight is the most recent IVRS weight reported before a subject is dosed.

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

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

A subject's dosing compliance should be within 75 to 125% during each period. Compliance to study medication dosing will be calculated for the overall Treatment Period (Titration + Maintenance Periods).

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

Change #12

Section 8.1.2.2 Primary analysis of the primary efficacy variable for the EU

The following text was added:

Subjects with 0 seizures at Baseline will be missing their Percent Change from Baseline. Subjects with 0 seizures at Baseline will be considered non-responders.

Change #13

Section 8.1.3.1 Sensitivity analyses of the primary efficacy variable for the US

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using the Baseline observation-carried-forward approach. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced by the overall mean

ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG from the subject's respective treatment group. This will be applied for all subjects who discontinued early from the study.

- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued early from the study.

Repeat the primary analysis using the FAS for all subjects who have at least 24 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG (rather than at least 48 hours).

Was changed to:

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of modified standard data cleaning and reconciliation processes, early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

- Repeat the primary analysis for the PPS.
- Repeat the primary analysis for the FAS-SDV.
- Repeat the primary analysis for the first 244 subjects enrolled in the study using the FAS.
- Repeat the primary analysis for the first 244 subjects enrolled in the study using the FAS-SDV.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using the Baseline observation-carried-forward approach. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced by the overall mean ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG from the subject's respective treatment group. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued early from the study.

- Repeat the primary analysis for the FAS for all subjects who have at least 24 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG (rather than at least 48 hours).

Change #14

Section 8.1.3.2 Sensitivity analyses of the primary efficacy variable for the EU

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except subjects who discontinued from the study prior to performance of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will still be considered non-responders, and subjects who discontinued from the study early for any other reason will be considered responders instead of missing.
- Repeat the primary analysis using the FAS, except all subjects who discontinued from the study early will be considered non-responders.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group, including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details provided in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued from the study early, and the imputed End-of-Maintenance Period ADF of partial-onset seizures will be used to determine whether a subject is a responder.
- Repeat the primary analysis using the FAS for all subjects who have at least 24 hours of interpretable recordings during both the end of Baseline Period video-EEG and the end of Maintenance Period video-EEG (rather than 48 hours). Noting that subjects who withdraw or drop out before the first 24 hours of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non-responders and will be included in the analysis; all other subjects will be missing and will not be included in this analysis.

Was changed to:

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of modified standard data cleaning and reconciliation processes, early discontinuations, protocol deviations, and operational bias on this primary endpoint. All sensitivity analyses require at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG, unless otherwise noted. Sensitivity analyses are as follows:

- Repeat the primary analysis for the PPS.

- Repeat the primary analysis for the FAS-SDV.
- Repeat the primary analysis for the first 244 subjects enrolled in the study using the FAS.
- Repeat the primary analysis for the first 244 subjects enrolled in the study using the FAS-SDV.
- Repeat the primary analysis for the FAS, except subjects who discontinued from the study prior to performance of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will still be considered non-responders, and subjects who discontinued from the study early for any other reason will be considered responders instead of missing.
- Repeat the primary analysis for the FAS, except all subjects who discontinued from the study early will be considered non-responders.
- Repeat the primary analysis for the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment group, including age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) and other appropriate variables (details provided in Section 8.1.3.3) using Monotone regression. This will be applied for all subjects who discontinued from the study early, and the imputed End-of-Maintenance Period ADF of partial-onset seizures will be used to determine whether a subject is a responder.
- Repeat the primary analysis for the FAS for all subjects who have at least 24 hours of interpretable recordings during both the end of Baseline Period video-EEG and the end of Maintenance Period video-EEG (rather than 48 hours). Noting that subjects who withdraw or drop out before the first 24 hours of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non-responders and will be included in the analysis; all other subjects will be missing and will not be included in this analysis.

Change #15

Section 8.2 Statistical analysis of the secondary efficacy variables:

The analyses of the secondary efficacy variables are based on the percent and absolute change in ADF of electrographic partial-onset seizures from baseline (defined in Sections 3.2.10 and 3.2.15).

Was changed to:

The analyses of the secondary efficacy variables are based on the percent and absolute change in ADF of electrographic partial-onset seizures from baseline (defined in Sections 3.2.10 and 3.2.15) and will be analyzed for the FAS unless otherwise noted; in addition, they will be analyzed for the FAS-SDV for sensitivity purposes.

Change #16

Section 8.2.1 Percent and absolute change in ADF of electrographic partial-onset seizures

A summary of the ADF of electrographic partial-onset seizures (defined in Section 3.2.10) from the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG will be presented by treatment group and by age group.

A summary of the percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG (defined in Sections 3.2.11 and 3.2.12) will be presented by treatment group.

Was changed to:

A summary of the ADF of electrographic partial-onset seizures (defined in Section 3.2.10) from the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG will be presented by treatment group for the FAS and the PPS and by age group for the FAS.

The summary of the ADF of electrographic partial-onset seizures will also be presented by treatment group on all subjects who have at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG for the FAS, the FAS-SDV, the PPS, and for the first 244 subjects enrolled in the study for the FAS and for the FAS-SDV.

A summary of the percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG (defined in Sections 3.2.11 and 3.2.12) will be presented by treatment group for the FAS.

The summary (absolute, percent and absolute change) of the ADF of electrographic partial-onset seizures will also be presented on all subjects who have at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Change #17

Section 8.2.5 Proportion of subjects who achieved seizure-free status

For subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG, the number and percentage of subjects who achieved “seizure-free” status from all seizure types, and from partial-onset seizure types only (defined in Section 3.2.15) will be tabulated and presented by treatment group for both the FAS and the PPS.

Was changed to:

For subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG, the number and percentage of subjects who achieved “seizure-free” status from all seizure types, and from partial-onset seizure types only (defined in Section 3.2.15) will be tabulated and presented by treatment group for the FAS, the FAS-SDV and the PPS.

Change #18

Section 8.3.3.1 Pediatric Quality of Life Inventory (PedsQL) Ages 1-12 Months

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions. The PedsQL will be administered only in countries where a translated version is available and will be completed at Visit 3, Visit 6, and at ETV in case of early termination. The version of the PedsQL used at

Visit 3 should be consistent with the subject's age at Visit 3 and should be maintained for each subject for the duration of the study. Section 3.2.16 details how the scores for the core domains are calculated.

The PedsQL completed at Visit 3 will be considered Baseline as it is expected that this will be completed prior to the first dose of study medication.

Was changed to:

The multidimensional PedsQL 1-12 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 5 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 1-12 months data will be listed.

Change #19

Section 8.3.3.2 Pediatric Quality of Life Inventory (PedsQL) Ages 13-24 Months

The multidimensional PedsQL 13-24 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score and each of the 5 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 13-24 months data will be listed.

Was changed to:

The multidimensional PedsQL 13-24 months generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 5 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 13-24 months data will be listed.

Change #20

Section 8.3.3.3 Pediatric Quality of Life Inventory (PedsQL) Ages 2-4 Years

The multidimensional PedsQL 2-4 years generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score and each of the 4 scale scores will be summarized for each visit, as appropriate, by treatment group. In addition, for this age group, a psychosocial health score (a combination of emotional, social and school functioning questions) will be calculated for each subject and summarized for each visit and Last Visit by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 2-4 years data will be listed.

Was changed to:

The multidimensional PedsQL 2-4 years generic core scales encompass the following core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

Calculated values and changes from Baseline for the total scale score (all scales), the psychosocial health summary score, the physical health summary score and each of the 4 scale scores will be summarized for each visit, as appropriate, by treatment group. A change from Baseline will only be calculated if the same version of the PedsQL was completed at Baseline and at the corresponding post-Baseline visit.

All PedsQL 2-4 years data will be listed.

Change #21

Section 9.1 Descriptive statistics for LCM plasma concentration

The paragraph 3 was updated as:

Summary tables of LCM plasma concentrations will be presented by treatment group, visit including the Last Visit and time point for the PK-PPS. Summaries will also be performed by LCM maintenance dose level and repeated by LCM maintenance dose level and age group.

Change #22

Section 10.2 Adverse events

The following text was added:

Additional subject data listings will be presented for PDILI-related TEAEs, deaths, and coronavirus-related AEs.

Change #23

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

MedDRA Preferred Terms “Alanine aminotransferase increased” and “Aspartate aminotransferase increased” have been added, duplicates have been removed, and Preferred Terms have been arranged in alphabetical order.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

Approval Signatures

Name: sp0967-sap-amend-2

Version: 2.0

Document Number: CLIN-000144485

Title: SP0967 Statistical Analysis Plan Amendment 2

Approved Date: 07 May 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 07-May-2020 15:17:07 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 07-May-2020 15:23:32 GMT+0000