STATISTICAL ANALYSIS PLAN

Study: EP0009

Product: Lacosamide

A MULTICENTER, OPEN-LABEL, UNCONTROLLED, LONG-TERM, EXTENSION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN JAPANESE AND CHINESE ADULTS WITH PARTIAL-ONSET SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION
PHASE 3

SAP/Amendment Number	Date
Final SAP	<12 Sep 2014>

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

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LIST OF ABBREVIATIONS

AE(s)	Adverse event(s)
AED(s)	Antiepileptic drug(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRF	Case Report Form
ECG(s)	Electrocardiogram(s)
eCRF	Electronic Case Report form
EEG	Electroencephalogram
FAS	Full Analysis Set
ICF	Informed consent form
ILAE	International League Against Epilepsy
LCM	Lacosamide
LFT	Lever function test
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred term
SAE(s)	Serious adverse event(s)
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QTcP	QT interval corrected using the population
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SS	Safety Set
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical principals that are applied for the analyses as well as tables and listings that are foreseen for this study. Tables or listings might be added or slightly modified for the purpose of readability or clarification of results that might have been seen during the process of analyzing the data. Changes in the statistical methodology result in an SAP amendment.

This SAP should be read in conjunction with the following documents that provide all necessary background information and rationale for the current study and its design.

1) Finalized Study Protocol Amendment
2) Electronic Case Report Form (eCRF)

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objectives

The primary objectives of this study are the following:

- To evaluate the safety and tolerability of long-term administration of lacosamide (LCM) at doses up to 400mg/day in Japanese and Chinese adults with epilepsy who have completed the Treatment and Transition Period of EP0008
- To allow subjects who had completed the Treatment and Transition Periods of EP0008 to receive LCM

2.1.2 Secondary objective

The secondary objective of this study is the following:

- To evaluate the efficacy of long-term administration of LCM at doses up to 400mg/day in Japanese and Chinese adults with epilepsy who have completed the Treatment and Transition Periods of EP0008

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

The primary safety variables are the following:

- Adverse events (AEs) reported spontaneously by the subject or observed by the investigator
- Subject withdrawals due to AEs

2.2.1.2 Other safety variables

The other safety variables are the following:

- Changes in hematology, clinical chemistry, and urinalysis parameters
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (ie, blood pressure, pulse rate)

- Changes in body weight

2.2.2 Efficacy variables

2.2.2.1 Primary efficacy variables

No primary efficacy variables are defined for EP0009.

2.2.2.2 Secondary efficacy variables

The secondary efficacy variables are the following:

- Percent change from Baseline in partial-onset seizure frequency per 28 days, where Baseline is defined as the Baseline Period of EP0008
- 50% response, where a responder is a subject experiencing a ≥50% reduction from Baseline in partial-onset seizure frequency per 28 days, and Baseline is defined as the Baseline Period of EP0008

2.2.2.3 Other efficacy variables

Other efficacy variables are the following:

- 75% response, where a responder is a subject experiencing a ≥75% reduction from Baseline in partial-onset seizure frequency per 28 days and Baseline is defined as the Baseline Period of EP0008
- Subjects who achieved "seizure-free" status (yes/no)
- Percentage of seizure-free days
- Subjects who are changed to LCM monotherapy for at least 6 months
- Subjects who are changed to LCM monotherapy for at least 12 months

2.3 Study design and conduct

EP0009 is a Phase 3, multicenter, open-label, uncontrolled, extension study designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as adjunctive therapy at doses up to 400mg/day in Japanese and Chinese adults with partial-onset seizures with or without secondary generalization who have completed the Treatment and Transition Periods of EP0008 and chose to enroll in EP0009.

Visit 1 of EP0009 is the same as the Final Visit of EP0008. Visits 2 through 4 of EP0009 will occur at 4-week intervals relative to the date of Visit 1. Beginning with Visit 5, each visit will occur at 12-week intervals relative to the date of Visit 1 until the End-of-Study/Withdrawal Visit.

At the completion of EP0008, all subjects who choose to enroll in EP0009 will be taking a dose of LCM 200mg/day. During the EP0009 Treatment Period, the investigator will be allowed to increase or decrease the doses of LCM and/or up to 3 concomitant antiepileptic drug(s) (AED[s]) to optimize tolerability and seizure reduction for each subject. The LCM dose may be decreased to 100mg/day or increased, no faster than 100mg/day per week, up to 400mg/day. Changes in concomitant AED(s) will be allowed only if the LCM dose has been stable for the previous 4 weeks; LCM dose must remain stable during changes to concomitant AED(s). Subjects may take no more than 3 concomitant AEDs except when temporary (≤12 weeks) use of an additional AED is required to switch to a new AED (ie, taper from old AED during titration of a new

AED). New AED(s) may be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. The concomitant AED(s) can be carefully tapered or discontinued at the discretion of the investigator. Monotherapy with LCM is permitted. Increasing the dose of LCM and/or concomitant AED(s), as well as the addition of a new AED, should be done at a visit (scheduled or unscheduled).

At the end of the Treatment Period, an End-of-Study Visit will be required. If subjects prematurely withdraw from the study, a Withdrawal Visit will be required. Subjects who complete the Treatment Period and choose not to continue on to commercial LCM treatment, and subjects who prematurely withdraw from the study, will enter a Taper Period. During the Taper Period, subjects receiving doses greater than LCM 200mg/day at the End-of-Study/Withdrawal Visit should be tapered off gradually at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that safety concerns require more rapid withdrawal of LCM. UCB (or designee) should be contacted if a more rapid withdrawal is required. A slower taper (e.g., LCM 100mg/day per week) is permitted, if medically necessary. Subjects receiving doses of LCM 200mg/day or lower at the End-of-Study/Withdrawal Visit are not required to taper off LCM. A Final Visit will be required 2 weeks after final LCM dose. Subjects who complete the Treatment Period and choose to continue on to commercial LCM treatment are not required to enter the Taper Period to taper off LCM or to return for a Final Visit; the End-of-Study Visit will be the last visit for these subjects. If LCM is not commercially available in a subject's country at the time the study closes, access to LCM will be provided according to local laws.

At selected sites, Japanese subjects may participate in an additional study (EP0024) with the intravenous formulation of LCM without withdrawing from EP0009. The study period of EP0024 will be included in that of EP0009. Subjects will continue to receive their current dose of LCM at the time of entry and remain stable for the duration of EP0024. Subjects who complete or withdraw from EP0024 will be given the opportunity to resume their participation in EP0009 with oral LCM treatment. In the event that a subject withdraws from EP0024 and is required to taper off LCM, the subject will return to EP0009 and taper using LCM tablets. Adverse events and concomitant treatment(s)/medication(s) that occur or were administered during EP0024 will be recorded in EP0024. Ongoing AEs and concomitant medication(s)/medical procedure(s) originating from the EP0024 will be followed in EP0009 until resolution or until stable. Where possible, data updates related to the resolution of ongoing AEs and concomitant medication(s)/medical procedure(s) from EP0024 will be reported in the EP0024 database (eg, updates are made in the EP0024 databases until the database is locked). All other data reported for EP0024 will be captured in the EP0024 database. Per the EP0024 protocol, the study (EP0024) will require hospitalization. Hospitalization for study participation does not need to be reported as an SAE.

2.4 Determination of sample size

No formal sample size determination has been performed because EP0009 is an extension study. Approximately 378 subjects, ie, 70% of subjects who were randomized in EP0008, are anticipated to participate in this extension study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Datasets will be analyzed using SAS version 9.1.3 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the safety and efficacy results.

For categorical parameters, the number and percentages of subjects in each category will be presented at the relevant time point. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts and 100% will be presented as an integer.

For continuous parameters, descriptive statistics will include number of the subjects, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the CRF. The mean, SD, median will be reported to one more decimal place, than the raw data recorded in the CRF. In general, the maximum number of decimal places reported should be 4 for any summary statistics.

Subjects who withdraw early from the study will be evaluated based on the data collected at each visit attended or period entered. Data summaries will be presented overall and by randomized dose in EP0008 unless otherwise specified. Additionally, summaries will be presented separately by country.

3.2 General study level definition

3.2.1 Relative day

Relative day is defined as the day relative to the first dose in EP0009 of LCM.

- If the start date of an event occurred prior to the first dose of LCM in EP0009, the relative day is calculated as start date minus first LCM dose date. In subject data listings, relative days based on this situation will be preceded by a "-".
- If the start date of an event occurred on or after the first dose of LCM but prior to or on the last dose of LCM in EP0009, the relative day is calculated as start date minus first LCM dose date + 1.
- If the start date of an event occurred after the date of last dose of LCM in EP0009, the relative day is calculated as start date minus last dose date. In subject data listings, relative days based on this situation will be preceded by a "+".

3.2.2 Analysis time point

For analysis purposes, the Treatment Period is defined as the period of time from the first dose of study drug during the EP0009 study to the date of last dose of study drug or the date of ESV/WV, whichever occurs later. The Treatment Period includes time while treated with LCM during the protocol-defined Taper Period if the subject enters the Taper Period.

The Post-Treatment Period is defined as the treatment-free observational period after the Treatment Period. It starts one day after the end date of the Treatment Period and ends on the date of the final clinic visit or date of last contact with the subject, whichever is later. Data for

safety parameters evaluated at clinic visits (ie, laboratory, ECG, vital signs, weight, physical exam, and neurological exam) will be summarized for each visit during the Treatment Period. Additionally, the minimum and maximum values during the Treatment Period will be summarized. Repeated or unscheduled assessments will not be included in the by-visit summaries but will be considered when determining the minimum and maximum Treatment Period values.

Data from the Final Visit (2 weeks after final LCM dose) will be reported separately on by-visit summaries of safety parameters evaluated at clinic visits. It should be noted that all subjects will not have completed a Final Visit. Subjects completing the study and continuing on commercially available LCM do not require a Final Visit per the protocol.

3.2.3 Completer cohort

A completer cohort will be defined as the subset of subjects in the FAS that were enrolled and treated with LCM for a specified duration of time and have seizure diary data available for the duration of the cohort. For example, a 6-month completer cohort consists of subjects enrolled and treated with LCM for at least 6 months and have efficacy data through at least 1-year exposure where a month is defined as 28 days. EP0009 will last 3 years, so 6-month completer cohort, 12-month completer cohort, 18- month completer cohort, 24-month completer cohort, 30-month completer cohort, and 36-month completer cohort will be defined in this study.

3.3 Definition of Baseline values

Unless otherwise specified, Baseline will be defined from the Baseline values of EP0008and will be taken directly from EP0008 data sets (ie, not reprogrammed in EP0009).

For Baseline seizure frequencies, the partial-onset seizures per 28-days derived during the Baseline Period in EP0008 will be used. The number of lifetime AEDs from EP0008 and the number of concomitant AEDs taken during EP0008 will also be used.

For quantitative ECGs, Baseline was defined as the average of the 3 ECG measurements taken at Visit 3 of EP0008. If a subject had less than 3 ECG measurements on the day of Visit 3 of EP0008, Baseline was to be defined as the average of the available ECGs on the day of Visit 3 of EP0008. If no ECGs were available on the day of Visit 3 of EP0008, Baseline was not defined for ECG assessments.

For laboratory and vital sign data, Baseline was the last non-missing evaluation prior to the first dose of intake of the study drug in EP0008.

3.4 Protocol deviations

The data will be reviewed to identify important protocol deviations. Important protocol deviations will be identified and documented prior to database snapshot for interim reports and database lock for the final analysis based on predefined criteria. Important deviations will be categorized as follows:

- Inclusion criteria
- Exclusion criteria
- Withdrawal criteria
- Prohibited medications
- Procedure non-compliance

- Other

A list of subjects with important protocol deviations will be agreed upon and documented prior to database lock.

3.5 Analysis sets

3.5.1 All Subjects Screened

All subjects screened will consist of all subjects who signed the informed consent form (ICF).

3.5.2 Safety Set

The Safety Set (SS) will include all enrolled subjects in EP0009 who took at least 1 dose of LCM in EP0009.

3.5.3 Full Analysis Set

The analysis set for the efficacy variables will be the Full Analysis Set (FAS) and will include all subjects in the SS having at least 1 day with available seizure diary data in EP0009.

3.6 Treatment assignment and treatment group

All subjects treated in EP0009 received LCM at doses ranging between 100mg/day to 400mg/day. A subject's LCM dose may be decreased to 100mg/day or increased, no faster than 100mg/day per week, up to 400mg/day. In terms of results presentation, summaries will present subjects overall and by randomized dose in EP0008: placebo, LCM 200mg/day, or LCM 400mg/day, unless otherwise specified.

3.7 Center pooling strategy

For the purpose of the summaries and analyses, the term 'Center' will be used to define each site.

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

Descriptive summaries will not be presented by individual center. Subject data listing will provide data sorted by country and individual center.

3.8 Coding dictionaries

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version SEP/2013.

All coding will be performed prior to database lock.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

This section is not applicable.

4.2 Handling of dropouts or missing data

For by-visit analyses, data from the Withdrawal Visit will be presented with data corresponding to the next scheduled visit for the subject.

Due to the potential for missing number of seizures for a given diary date, seizure frequency will be calculated using only the number of days for which seizure data is provided.

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

- Missing start day, but month and year present: If the start date of study treatment occurred in the same month and year as the occurrence of the event/medication, the start day of the event/concomitant medication will be assigned to the day of first intake of study treatment in order to treat the adverse event and medication as treatment-emergent and concomitant, respectively. 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 date of trial medication occurred in the same year as the occurrence of the event/medication, the start day and month will be assigned to the date of first intake of study treatment in order to treat the adverse event and medication as treatment-emergent and concomitant, respectively. Otherwise the start day and month will be set to January 1st.
- Start date is completely unknown: The start date of the event/concomitant medication will be assigned to the date of first intake of study treatment.
- 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 or the date equivalent to 30 days after last intake of study treatment.
- End date is completely unknown: The end date will not be imputed.

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

Relative day is not calculated for partial dates in cases where relative day is shown in a subject listing. In such cases, relative day should be left blank in the subject data listings.

Subjects participating in EP0024 while also enrolled in EP0009 will have missing data for seizure frequency and drug dosing while participating in the EP0024 trial. As the duration of the EP0024 study will be short (3-7 days), no imputation for data missing due to participation in EP0024 will be performed. Subjects will be assigned the same dose in EP0024 as that assigned in EP0009 for the two weeks prior to the start of EP0024. As such, time during the EP0024 study will not be subtracted from the exposure calculations (eg, exposure will be from the start of LCM treatment in the EP0009 study until the date of last dose of LCM in EP0009).

For the calculation of variables related to seizure frequency, the dates during participation in EP0024 will be considered as not done for the purpose of efficacy analyses for trial EP0009 (eg, these dates will not be considered as days evaluated for seizure frequency). Due to the short nature of the EP0024 study, only a few days of seizure frequency data are expected to be missing

due to participation in EP0024 unless otherwise specified (eg, for the evaluation of seizure freedom).

4.3 Interim analyses and data monitoring

No formal interim analysis is planned. However, data will be reported prior to the completion of this study to support regulatory submissions. At a minimum, 2 interim reports are planned after all enrolled Japanese subjects complete through Visit 5 (Week 24) and after all enrolled Japanese subjects complete through Visit 7 (Week 48). All analyses described in this SAP will be presented at each interim analysis for regulatory reporting.

4.4 Multicenter studies

Descriptive summaries for individual sites will not be presented due to the low number of expected subjects per site. However, subject data listings will provide data grouped by country and individual site.

4.5 Multiple comparisons/multiplicity

This section is not applicable.

4.6 Use of an efficacy subset of subjects

Selected efficacy analyses will be performed for the completer cohorts defined in Section 3.2.3.

4.7 Examination of subgroups

Unless otherwise noted, all tabular data summaries will be presented overall and by country (Japan, China).

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Summary tables of subject disposition will be provided overall, by EP0008 randomized dose and by country separately as follows:

- The number of subjects in the SS, and in the FAS will be presented. The date of the first visit for the first subject, date of the last visit for the last subject, and the number of subjects screened will also be included. (Analysis population: All Subjects Screened)
- The number and percentage of subjects entering, completing, ongoing, and discontinuing the study with associated reasons for discontinuation. The number and percentage of ongoing subjects will be displayed at the interim analyses only. (Analysis population: SS and FAS)
- A by-subject listing of analysis population classification (Analysis population: SS)

The following listing will be provided:

- Subject disposition status, including the date of informed consent, screening result, date of study completing/discontinuation, and reason for premature discontinuation. (Analysis population: SS)
- A by-subject listing of subjects who did not meet study eligibility criteria (Analysis population: All Subjects Screened)

- A by-subject listing of analysis population classification (Analysis population: SS)

5.2 Protocol deviations

A summary table and listing of important protocol deviations will be provided for the SS as follows:

- The number and percentage of subjects with no important protocol deviations and with at least 1 important protocol deviation in each of the categories defined in Section 3.4 will be summarized overall, by EP0008 randomized treatment group, and by country separately.
- A by-subject listing of important protocol deviations will be presented.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, demographics, baseline characteristics, medical history, concomitant disease, and concomitant medications will be summarized for the SS and FAS overall, by EP0008 randomized treatment group, and by country separately.

Subject listings of demographics, baseline characteristics, medical history, concomitant diseases, and concomitant medication will be displayed for the SS.

6.1 Demographics

Summary statistics or the number and percentage for each category of demographic information will be presented as follows:

- A summary of demographics data including gender, age (years), age category (≤18, >18 to <65, ≥65 years) (<16, ≥16 to <65, ≥65 years), ethnicity (Hispanic or Latino, and not Hispanic or Latino), race group (American Indian/ Alaskan native, Asian, Black, Native Hawaiian or other Pacific Islander, White, and Other/mixed), race, racial subgroup (Chinese or Japanese), height, weight, body mass index (BMI, kg/m^2), BMI category (<18.5, ≥18.5 to <25, ≥25 to <30, and ≥30 kg/m^2), number of lifetime AEDs, number of concomitant AEDs during EP0008, and Baseline partial-onset seizure frequencies per 28 days will be provided overall, by EP0008 randomized treatment group, and by country separately.
- A by-subject listing of demographic data.

Gender, race, ethnicity, racial subgroup, height, weight, and BMI will betaken directly from EP0008 datasets and not programmed. Age will be relative to the date of informed consent for EP0009.

6.2 Other Baseline characteristics

Summary statistics or the number and percentage for each category of baseline characteristics as reported at Visit 1 of EP0008 will be provided as follows:

- A summary of the diagnoses of primary disease, including time since diagnosis of epilepsy (in years) and etiology of epilepsy taken from EP0008 will be provided.

  In EP0008, time since first diagnosis was calculated using all available information; partial dates was completed using the earliest calendar date based on the partial date provided.

In EP0008, time since the first diagnosis (years) was calculated as (year and month of informed consent date – year and month of the first diagnosis) / 365.25. Month and year of the first epilepsy diagnosis are collected on the CRF. To calculate the time since first epilepsy diagnosis at Visit 1 of EP0008, a complete date will be imputed as follows:

- Month and year present assign the 1st day of the month, the subject's birthday, or the date of the first seizure, whichever is later in the month.
- Missing the month, but year present assign January 1st of the year, the subject's birthday, or the date of the first seizure, whichever is later in the year.
- Both month and year are missing, no imputation will be done.

- A summary of International League Against Epilepsy (ILAE) seizure classification will be provided.

  The types of partial seizures experienced will be summarized using the ILAE classification system.

- A summary of classification of epileptic syndromes.
- A by-subject listing of other Baseline characteristics.

6.3 Medical history and concomitant disease

Medical history and concomitant diseases will be as reported as of Visit 1 of EP0008.

Concomitant diseases are medical history events which were ongoing at Visit 1 of EP0008.

Summary tables of medical history and concomitant diseases will be provided for the SS as follows:

- A summary of medical history by MedDRA system organ class (SOC) and preferred term (PT) will be presented overall, by EP0008 randomized treatment group, and country separately.
- A summary of concomitant disease by MedDRA system organ class (SOC) and preferred term (PT) will be presented overall, by EP0008 randomized treatment group, and country separately.
- A by-subject listing of medical history.
- A by-subject listing of concomitant diseases.
- A by-subject listing of procedure history.

6.4 Concomitant medications

Concomitant medications will be defined as any medications taken concurrent with LCM if the start date was prior to the first dose with ongoing status, or the start date was on or after the date of first dose of study drug in EP0009. Medications with a missing start date, whose stop date is either unknown or after the date of the first dose of study drug, will be considered concomitant.

Summary tables will be provided for the SS and FAS as follows:

- A summary of concomitant medications (excluding AEDs) taken during Treatment Period will be provided by level 1 and level 2 ATC code. The tables will be presented overall, by EP0008 randomized treatment group, and by country separately.

- A summary of concomitant AEDs taken during the Treatment Period will be provided by Level 4 ATC code and preferred medication name. The tables will be presented overall, by EP0008 randomized treatment group, and by country separately.
- A by-subject listing of concomitant AEDs (Analysis population: SS)
- A by-subject listing of concomitant medications (non-AEDs) (Analysis population: SS)

7 MEASUREMENTS OF TREATMENT COMPLIANCE

LCM dosing compliance will be evaluated through the review of important protocol deviations classified under LCM Dosing Regimen.

8 SAFETY ANALYSES

All safety analyses will be performed on the SS.

8.1 Extent of exposure

Overall exposure to LCM in days is calculated as the date of last administration of LCM minus the date of first administration in EP0009 plus 1. Subject-years of exposure will be calculated as the number of days of exposure, divided by 365.25. Gaps in LCM treatment or days on the LCM dosing log CRF with unknown dosing will not be subtracted from the overall exposure days and subject-years of exposure.

The maximum daily dose will be calculated as the highest total daily dose the subject received during the treatment period.

LCM modal dose (mg/day) will be defined as the daily LCM dose the subject received for the longest duration during the treatment period in EP0009. A modal dose calculated as 50mg/day will be presented with 100mg/day. For any modal dose greater than 100mg/day falling between 2 consecutive categories, the modal dose will be presented with the lower of the consecutive categories. For example, 150mg/day will be presented with the 100mg/day group. The modal dose calculation is based on the number of days a subject was on a given daily dose. Gaps in LCM dosing will be excluded from the determination of modal dose (ie, no imputation for days with missing dosing log information will be performed).

The following exposure summaries and a listing will be produced:

- Summary statistics for study treatment duration (days) by modal dose and overall.
- Number of subjects and subject-years of study treatment duration by cumulative time intervals (ie, >0, >6, >12, >18, >24, >30, and >36 months, where one month is defined as 28 days) and modal dose.
- Number and percentage of subjects within each LCM treatment duration category by modal dose, maximum daily dose, and overall. LCM treatment duration categories (days) are as follows: 1 to 14; 15 to 28; 29 to 56; 57 to 84; 85 to 168; 169to 336; 337 to 672; 673 to 1008; ≥1009 to 1344; 1345 to 1680; 1681 to 2016; ≥2017; any duration (total of durations).
- Summary statistics for overall treatment duration (days), modal dose (mg/day), and maximum daily dose (mg/day) will be presented by EP0008 randomized treatment group and overall.

- A by-subject listing of LCM dosing.

8.2 Adverse events

TEAE is defined as an event starting on or after the date of first dose of LCM in this study and within 30 days of the last LCM dose, or whose severity worsen on or after the date of first LCM dosing in this study and within 30 days of the last LCM dose.

TEAEs will be coded using MedDRA and tabulated by SOC and PT. All summaries will be sorted alphabetically by SOC and by frequency of events in the overall column within the SOC, starting with the most frequent event unless otherwise specified.

The following summary tables of TEAEs will be provided overall, by EP0008 randomized treatment group, and by country separately. For the summary tables of TEAEs onset during the Treatment Period will be further presented overall, by 6month interval, by EP0008 randomized treatment group, by country, and follows as well:

- Overview summaries of TEAEs with onset during the Treatment Period and events during the Post-Treatmrent Period will be presented. They will include the number and percentage of subjects with at least 1 TEAE, at least 1 serious TEAE, at least 1 TEAE leading to early withdrawal, drug-related TEAEs, at least 1 severe TEAE, and death.
- Summary of the incidence of TEAEs with onset during the Treatment Period by SOC and PT.
- Summary of the incidence of TEAEs with onset during the Treatment Period by SOC, PT, and maximum intensity.
- Summary of the incidence of TEAEs with onset during the Treatment by SOC, PT, and relationship.
- Summary of the incidence of serious TEAEs with onset during the Treatment by SOC and PT.
- Summary of the incidence of non-serious TEAEs by SOC and PT. The occurrence of non-serious TEAEs is only presented with incidence ≥ 5%.
- Summary of the incidence of TEAEs leading to discontinuation with onset during the Treatment Period by SOC and PT.
- Summary of the incidence of other significant TEAEs (Section 13.1) with onset during the Treatment Period by SOC and PT.
- Summary of incidence of TEAEs with onset during the Treatment Period per 100 person-months of exposure.
- A summary of subject numbers of subjects with TEAEs with an onset during the Treatment Period.
- A summary of subject numbers of serious TEAEs with an onset during the Treatment Period.
- A summary of subject numbers of TEAEs with an onset during the Treatment Period leading to discontinuation.
- A by-subject listing of all TEAEs; events with onset during the Post-Treatment Period will be identified.

- A by-subject listing for all deaths
- Glossary of MedDRA terms and associated investigator's terms for adverse events.

8.3 Clinical laboratory evaluations

For continuous laboratory measurements, including hematology, clinical chemistry, and urinalysis, a summary using descriptive statistics of the actual values and their change from Baseline (where Baseline is from the previous trial as defined in Section 3.3) will be presented at each visit, the last visit value, the minimum value, and the maximum value during the Treatment Period. For white blood cell differentials, both of absolute values and percentages of the white blood cell count will be analyzed. When analyzing categorical data, the number and percentage of subjects in each category will be presented. In addition, shift tables will be used to evaluate the number and percentage of subjects having a different Treatment Period status (low, normal, and high) when compared to their baseline status from EP0008.

Repeated or unscheduled laboratory assessments during the study will not be presented for each visit summary, but will be considered when determining the last visit value, minimum value, and maximum value during the Treatment Period and when determining treatment emergent marked abnormality.

Categorical urinalysis parameters (excluding urine glucose, urine ketones, and urine protein) will be presented in listings only.

The number and percentage of subjects with treatment-emergent marked laboratory abnormalities (hematology and clinical chemistry) as defined in Section 13 will be summarized by laboratory parameters. Treatment-emergent is defined as meeting the marked abnormality criteria during EP0009 Treatment Period but not meeting the criteria during Baseline of EP0008. Subject numbers for subjects meeting the marked abnormality criteria will also be presented.

A subject data listing will be provided for all laboratory data. Values outside the normal range will be flagged within the listing. A subject data listing will also be provided for all treatment-emergent marked laboratory abnormalities and will include all lab values for those subjects experiencing the marked abnormality.

The following summaries and listings will be provided:

- A summary of each laboratory parameter and change from Baseline of EP0008.
- A shift table based on the normal range for each lab parameter will be presented by Treatment Period endpoint value relative to Baseline of EP0008.
- A summary of incidence of treatment-emergent marked abnormalities presented by scheduled visit and for the entire Treatment Period (including unscheduled visits) during the Treatment Period for the laboratory parameters, hematology and clinical chemistry.
- A shift table that will cross-tabulate Baseline value of EP0008 by maximum value during the Treatment Period (including unscheduled visits) will be presented for liver function tests (LFTs) which include alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, ATL, and total bilirubin based on abnormality.

The shift table that cross-tabulates Baseline versus maximum values during the Treatment Period in categories of <1 x ULN, 1 to <2 x ULN, 2 to <3 x ULN, ≥3 x ULN, and missing will be presented for the liver function tests.

- Subject numbers of treatment-emergent marked abnormalities during the Treatment Period for each laboratory parameter will be provided.

The summaries above will be provided overall, by EP0008 randomized treatment group, and by country separately.

- A by-subject listing of subjects with laboratory values.
- A by-subject listing of LFTs with pre-defined criteria.

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

8.4.1 Vital signs

Noninvasive pulse rate, systolic blood pressure, and diastolic blood pressure will be measured at visits with the subject in a sitting position after at least 3 minutes at rest, according to the tabular schedule of study procedures in the protocol. Summary statistics of the actual measurement and their changes from Baseline will be presented at each visit, the last visit value, the minimum value, and the maximum value during the Treatment Period.

Repeated or unscheduled vital sign assessments during the study will not be presented for each visit summary, but will be considered when determining the last visit value, minimum value, and maximum value during the Treatment Period and post-Baseline abnormal vital signs during Treatment Period.

The following summaries and a listing will be provided:

- A summary of observed blood pressure and pulse rates and changes from Baseline of EP0008.
- The number and percentage of subjects with post-Baseline abnormal vital signs during Treatment Period as defined in Section 13.

The summaries above will be provided overall, by EP0008 treatment group, and by country separately.

- A by-subject listing of vital signs. Abnormal vital signs will be flagged in the listing.

8.4.2 Electrocardiograms

For quantitative ECG measurements (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT intervals using Bazett and Fridericia methods), summary statistics of the actual measurement collected at Baseline and each Treatment Period visit (as well as change from Baseline) will be presented. Baseline is defined as the average of the 3 ECG measurements taken at Visit 3 in EP0008. In addition to Baseline and each Treatment Period visit, the last visit, minimum, and maximum values during the Treatment Period of EP0009 will be presented. Repeated or unscheduled ECG assessments during the study will not be presented for each visit summaries, but will be considered when determining the last visit value, minimum value, and maximum value during the Treatment Period and abnormal ECG values.

The Bazett corrected QT (QTcB) will be calculated as

$\text{QTcB} = \frac{\text{QT}}{\sqrt{\text{RR}}}$, where RR = 60/HR.

The Fridericia corrected QT (QTcF) will be calculated as

$\text{QTcF} = \frac{\text{QT}}{\sqrt[3]{RR}}$, where RR = 60/HR.

The following summaries and listings will be provided for the SS:

- A summary of ECG measurements (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT intervals using Bazett and Fridericia methods) and changes from Baseline of EP0008.
- The number and percentage of subjects with a QTc (using Bazett and Fridericia) of ≥500ms and an increase from Baseline of <30ms, 30 to <60ms, and ≥60ms will be summarized for each visit.
- The number and percentage of subjects with a maximum QTc of ≥500ms, a maximum increase in QTc from Baseline of <30ms, 30 to <60ms, and ≥60ms, a maximum post-Baseline QTc of ≥500ms or a maximum increase in QTc of ≥60ms, and a maximum post-Baseline QTc of ≥500ms and a maximum increase in QTc of ≥60ms will be summarized for each of the corrected QT interval formulas. Subjects with a QTc (Bazett and Fridericia) of ≥500ms or an increase from Baseline of ≥60ms will be listed.
- The number and percentage of subjects with PR interval values >200ms, >220ms, or >250ms, and the number and percentage of subjects with QRS interval values >100ms, >120ms, and >140ms will be presented. For these defined criteria, the number and percentage of subjects with treatment-emergent PR interval and/or QRS interval prolongation will also be presented. Treatment-emergent is defined as meeting the criteria at any Treatment Period visit (including unscheduled visits) during the Treatment Period and not meeting the same criteria during Baseline.
- Subject numbers for subjects with prolonged post-Baseline QTcB will be provided.
- Subject numbers for subjects with treatment-emergent PR interval prolongation will be provided.
- Subject numbers for subjects with treatment-emergent QRS interval prolongation will be provided.
- A summary of incidence of treatment-emergent abnormality 12-lead ECG findings after start of study drug for each visit and during the Treatment Period in EP0009.

The summaries above will be provided overall, by EP0008 randomized treatment group, and by country separately.

- A by-subject listing of 12-lead ECG data.
- A by-subject listing of abnormal 12-lead ECG data as defined in Section 13 .

8.4.3 Other safety variables

Body weight will be determined without shoes when the subject is wearing light clothing, and will be assessed according to the tabular schedule of study procedures.

The following summaries and listings will be provided:

- A summary of body weight and change from Baseline for each visit
- The number and percentage of subjects with Treatment Period abnormal body weight during the Treatment Period as defined in Section 13.

The summaries above will be provided overall, by EP0008 randomized treatment group, and by country separately.

- A subject listing of body weight and change from Baseline in body weight
- A subject listing of abnormal physical examination abnormalities
- A subject listing of neurological examination findings
- A subject listing of pregnancy test
- A subject listing of C-SSRS suicidality

9 EFFICACY ANALYSES

All efficacy variables are to be evaluated descriptively using FAS.

9.1 Statistical analysis of the primary efficacy variables

No primary efficacy variables are defined for EP0009.

9.2 Statistical analysis of the secondary efficacy variables

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

The following table and listing will be provided:

If a seizure cluster is reported, it will be assigned to the correct seizure type and the highest recorded daily number of seizures of that seizure type during the 28 days prior to the cluster event will be used as the imputed number of seizures for the day on which the cluster occurred. If no other seizures are recorded for that seizure type for the subject in the 28 days prior to the cluster event, the frequency will be set to 1 or the number of cluster episodes reported if more than 1 cluster event occurred on the same day.

9.2.1 Percent change in seizure frequency from Baseline to the Treatment Period

The percent change in partial-onset seizure frequency per 28 days from Baseline to the Treatment Period in 6-month interval is calculated by the following formula:

$$\text{Percent Change (\%)} = \frac{\text{[(Seizure frequency per 28 days in 6-month interval during the Treatment Period) - (Seizure frequency per 28 days during Baseline Period)]}}{\text{(Seizure frequency per 28 days during Baseline Period)}} \times 100$$

Descriptive statistics will be calculated for the percent change in partial-onset seizure frequency per 28 days from Baseline to the Treatment Period in 6-month specified interval during the Treatment Period, and overall.

The percent change in 28-day seizure frequency per 28 days from Baseline among each completer cohort will also be displayed. A subject must have been treated with LCM and have available seizure diary data for the interval for each interval (eg, 6-month completer cohort subjects must be enrolled and taking trial medication for at least 6 months and have available seizure diary data for the interval) to be included in the 6-month completer cohort (see Section 3.2.3 for definition of completer cohort).

- A summary of the percent change in partial-onset seizure frequency per 28 days from Baseline will be presented by 6-month interval and overall Treatment Period.
- A summary of the percent change in partial-onset seizure frequency per 28 days from Baseline among each complete cohort will be presented. For each completer cohort, the percent change in 28-day seizure frequency per 28 days from Baseline will be presented by 6-month time interval..

The summaries above will be provided overall, by EP0008 randomized treatment group, and by country separately.

- A by-subject listing of number of seizure, seizure frequency per 28 days and percent change from Baseline by 6-month interval and overall Treatment Period.

9.2.2 Response to treatment of at least 50% from Baseline to the Treatment Period

≥50% responders are defined as subjects who experience a ≥50% reduction in partial-onset seizure frequency per 28 days from Baseline to the 6-month interval or the Treatment Period which is defined at Section 9.2.1.

- The number and percentage of ≥50% responders in the partial-onset seizure frequency per 28 days from Baseline to the Treatment Period by 6-month interval and overall Treatment Period will be presented.
- The number and percentage of ≥50% responders among each completer cohort will be presented in a same way as above. For each completer cohort, the ≥50% response rate will be presented by 6-month time interval.

The summaries above will be provided overall, by EP0008 randomized treatment group, and by country separately.

- A by-subject listing of ≥50% responder categories by 6-month interval and overall Treatment Period.

9.3 Analysis of other efficacy variables

9.3.1 Response to treatment of at least 75% from Baseline to the Treatment Period

≥75% responders are defined as subjects who experience a ≥75% reduction of in the partial-onset seizure frequency per 28 days from Baseline to the 6-month time interval or the Treatment Period.

- ≥75% responders will also be summarized by the same manner as ≥50% responders, described in Section 9.2.2.
- The number and percentage of ≥75% responders in the partial-onset seizure frequency per 28 days from Baseline to the Treatment Period by 6-month interval and overall Treatment Period will be presented.
- The number and percentage of ≥75% responders among each completer cohort will be presented in a same way as above.

The summaries above will be provided overall, by EP0008 randomized treatment group, and by country separately.

- A by-subject listing of ≥75% responder categories by 6-month interval and overall Treatment Period.

9.3.2 Seizure-free status

A seizure-free status will be assessed for the duration of at least consecutive 6 months (182 days) and at least consecutive 12 months (365 days). Seizure-free is defined as a report of no seizures in the seizure diary on the CRF for the consecutive days where the subject was treated with LCM. Days in the seizure diary which are marked as "not done" on the CRF will not be counted as a seizure free day unless otherwise noted.

When subjects are in EP0024, the days should be treated as "not done" days for EP0009 but they should not disqualify a subject from being seizure free if they were in EP0024.

- The number and percentage of subjects who achieved seizure-free status (yes/no) for the duration of at least 6 months and at least 12 months will be presented overall, by completer cohort, by EP0008 randomized treatment group, and by country separately.
- A by-subject listing of seizure freedom data.

9.3.3 Percentage of seizure-free days

Percentage of seizure-free days is calculated as:

$$\text{Percentage of seizure free days} = \frac{\text{Seizure free days during time interval in the Treatment Period}}{\text{Number of days during time interval in the Treatment Period with available seizure diary data}} \times 100\%$$

Time interval is defined as 6-month interval for the first year and yearly intervals thereafter (at least 6 months, at least 12 months, at least 24, and at least 36 months).

- Summaries of the percentage of seizure-free days during the Treatment Period will be presented overall, by completer cohorts, EP0008 randomized treatment group, and by country separately.
- A summary of change in percentage of seizure-free days and change in percentage from Baseline from Baseline during the Treatment Period will be presented overall, by completer cohorts, by EP0008 randomized treatment group, and by country separately.

9.3.4 Subjects receiving LCM as monotherapy

Monotherapy is defined as when LCM only is used during the period with no other concomitant AEDs. If the subjects had a rescue medications of benzodiazepines which are used for the control of uncountable seizures due to clustering are not regarded as AEDs. Other AED rescues where an AED was taken for ≤1 day will also not disquality a subject from being on LCM monotherapy.

- The number and percentage of subjects achieving continuous LCM monotherapy for at least 6 months and at least 12 months at any time during the Treatment Period among subjects who were exposed to LCM for at least 6 months and at least 12 months during the Treatment Period will be presented overall, by EP0008 randomized treatment group, and by country separately.

10 PHARMACOKINETICS AND PHARMACODYNAMICS

This section is not applicable.

11 OTHER ANALYSES

Not applicable for this study.

12 REFERENCES

13 APPENDICES

13.1 List of Other Significant AEs

MedDRA Preferred Term
HEPATOTOXICITY RELATED TERMS
Hepatitis toxic
Hepatotoxicity
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
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation

MedDRA Preferred Term
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

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

13.2 Marked lab abnormalities

13.2.1 Hematology

Abnormality criteria to be applied in the assessment of laboratory parameter values are given below.

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional unit)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard unit)*
Hematocrit	<2y	%	≤27 >45	%	≤27 >45
	2y - <17y		≤29 >47		≤29 >47
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
Hemoglobin	<2y	g/dL	≤9.0 >15.0	g/L	≤90 >150
	2y - <17y		≤9.5 ≥16.0		≤95 >160
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
WBC/Leukocytes	All	10^9/L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0
Lymphocytes Absolute	<2y	10^9/L	<1.0 >9.8	G/L	<1.0 >9.8
	2y - <6y		<0.7 >6.9		<0.7 >6.9
	≥6y		<0.6 >5.0		<0.6 >5.0
Basophils	>1m	%	≥5.0	%	≥5.0
Basophils Absolute	>1m	10^9/L	≥0.4	G/L	≥0.4
Eosinophils	>1m	%	≥10	%	≥10
Eosinophils Absolute	>1m	10^9/L	≥1.0	G/L	≥1.0
Monocytes	>1m	%	≥20.0	%	≥20.0
Monocytes Absolute	>1m	10^9/L	≥2.0	G/L	≥2.0
Neutrophils Absolute	>1m	10^9/L	<1.5	G/L	<1.5
Platelets	>1m	10^9/L	≤100 ≥600	G/L	≤100 ≥600

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional unit)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard unit)*
RBC/ Erythrocytes	<2y	10^{12}/L	<3.0	T/L	<3.0
	≥2y		<3.5		<3.5

Abbreviations: ANC = absolute neutrophil count.

13.2.2 Chemistry

Abnormality criteria to be applied in the assessment of chemistry parameter values are given below.

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
AST (SGOT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
Alkaline Phosphatase	<4y	U/L	≥690	U/L	≥690
	4y - <10y		≥834		≥834
	10y - <17y		≥1761		≥1761
	≥17y		≥3.0 x ULN		≥3.0 x ULN
GGT	<6m	U/L	≥522	U/L	≥522
	6m - <1y		≥279		≥279
	1y - <13y		≥66		≥66
	13y - <17y		≥126		≥126
	≥17y		≥3.0 x ULN		≥3.0 x ULN
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	2m-<1y	g/dL	<3.0 >11.9	g/L	<30 >119
	1y - <17y		<4.3 >12.0		<43 >120
	≥17y		<4.3 >13.0		<43 >130
Albumin	<1y	g/dL	<1.6 >7.2	g/L	<16 >72
	≥1y - <17y		<2.4 >8.4		<24 >84
	≥17y		<2.6		<26

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
BUN	<1y	mg/dL	≥24	mmol/L	≥8.568
	1y - <17y		≥36		≥12.852
	≥17y		≥40		≥14.28
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y		>60		>10.02
Creatinine	1y - <10y	mg/dL	>1.2	umol/L	>106.8
	10y - <16y		>1.8		>159.12
	≥16y		≥2.0		≥176.8
Creatinine Clearance*	All	mL/min	<50	mL/s	<0.835
Bicarbonate	>1m - <17y	mEq/L	<15 >38	mmol/L	<15 >38
	≥17y		<18 >38		<18 >38
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <17y		<7.4 >11.7		<1.85 >2.925
	≥17y		≤7.6 ≥11.0		≤1.9 ≥2.75
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	1y - <17y		<1.8 >7.4		<0.5814 >2.3902
	≥17y		≤2.0 ≥6.0		≤0.646 ≥1.938
Potassium	<1y	mEq/L	≤3.0 ≥6.5	mmol/L	≤3.0 ≥6.5
	≥1y		≤3.0 ≥6.0		≤3.0 ≥6.0
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Glucose	>1m - <17y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99
	≥17y		<50 ≥200		<2.775 ≥11.1
Total Cholesterol	≥1y	mg/dL	>250	mmol/L	>6.475
LDL (calculated)	1y - <17y	mg/dL	>140	mmol/L	>3.626
	≥17y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y		>300		>3.39
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996
	1y - <13y		>6.5		>386.62
	13y - <17y		>8.6		>511.528
	≥17y		>9.5		>565.06
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y		≤3.8 ≥13.5		≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >4.5	g/L	<10 >45
	≥1y		<1.2 >5.3		<12 >53

ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein.

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

13.3 Vital sign assessments - abnormal

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

PARAMETER	*AGE RANGE*	*ABNORMALITY CRITERIA*
Pulse Rate (beats/minute)	<6m	<100 >180
	6m - <3y	<90 >150
	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120
	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	≤50 ≥105
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥105 and an increase from Baseline of ≥ 15
Respiratory Rate (breaths/minute)	<6m	<25 >55
	6m - <3y	<20 >45
	3y - <12y	<15 >35
	≥12y	<10 >25
Temperature	>1m	>101 ^{0}F (38.3 ^{0}C)

PARAMETER	*AGE RANGE*	*ABNORMALITY CRITERIA*
Body Weight	1m - <17y	<3% or >97% of the normal body weight growth curve ranges based on gender and the age of subject on date of weight assessment[a]
	≥17y	≥ 10% change from Baseline (an increase or a decrease)[a]

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

13.4 Electrocardiogram (ECG) – abnormal

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

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	≥500
	≥12y	≥500 or ≥60ms increase from Baseline
QTc(F) (ms)	<6m	>490, or >15% increase from Baseline
	6m-<3y	>440, or >15% increase from Baseline
	3y-<12y	>440, or >15% increase from Baseline
	≥12y- <17y	>440, or >15% increase from Baseline
	≥17y	≥500 or ≥60ms increase from Baseline
QTc(B) (ms)	<6m	>490, or >15% increase from Baseline
	6m-<3y	>450, or >15% increase from Baseline
	3y-<12y	>450, or >15% increase from Baseline
	≥12y- <17y	>450, or >15% increase from Baseline
	≥17y	≥500 or ≥60ms increase from Baseline
PR interval (ms)	<6m	>150, or ≥25% increase from Baseline
	6m-<3y	>170, or ≥25% increase from Baseline
	3y-<12y	>180, or ≥25% increase from Baseline
	≥12y - <17y	>200, or ≥25% increase from Baseline
	≥17y	Treatment-emergent value >200, >220, >250
QRS interval (ms)	<6m	>90, or ≥25% increase from Baseline
	6m-<3y	>90, or ≥25% increase from Baseline
	3y-<12y	>100, or ≥25% increase from Baseline
	≥12y - <17y	≥110, or ≥25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	<6m	<100, >180
	6m-<3y	<90, >150
	3y-<12y	<60, >130
	≥12y	<50, >120

Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline