STATISTICAL ANALYSIS PLAN

Study: EP0057

Product: Lacosamide

A MULTICENTER, OPEN-LABEL, LONG-TERM STUDY TO INVESTIGATE THE SAFETY OF CONVERSION TO LACOSAMIDE AT DOSES UP TO 600MG/DAY AS MONOTHERAPY IN JAPANESE ADULTS WITH PARTIAL-ONSET SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

SAP/Amendment Number	Date
Final SAP	<11 Apr 2014>
Final Amendment 1	<03 Sep 2015>
Final Amendment 2	<21 Apr 2016>

Confidentiality Statement

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	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
BMI	Body Mass Index
CI	Confidence interval
CT	Computed tomography
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
EEG	Electroencephalogram
ESV	End-of-Study Visit
ETV	End-of-Taper Visit
EWV	Early Withdrawal Visit
FAS	Full Analysis Set
GGT	Glutamiltransferase
ILAE	International League Against Epilepsy
IMP	Investigational medicinal product
LCM	Locosamide
LOE	Lack of efficacy
NDA	New drug application
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Monotherapy Visit
MRI	Magnetic resonance imaging
PK	Pharmacokinetic
PR	Pulse rate
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SPD	Specification of protocol deviation
SS	Safety Set
TEAE	Treatment-emergent adverse event

TEMA	Treatment-emergent marked laboratory abnormalities
ULN	Upper limit of normal
WHO-DRL	World Health Organization Drug Reference List

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical principles that are applied for the analyses as well as data presentations 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 be seen during the process of analyzing the data. Changes in the statistical methodology will result in a 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.

- Finalized Study Protocol Amendment, dated 09 October 2013
- Electronic Case Report Form (eCRF), dated 09 December 2013

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is to evaluate the long-term safety and tolerability of LCM 200mg/day to LCM 600mg/day taken in monotherapy in Japanese subjects who currently have partial-onset seizures with or without secondary generalization and who are treated with a single antiepileptic drug (AED) with marketing approval in Japan.

2.1.2 Secondary objectives

The secondary objectives are to evaluate the efficacy of LCM, and the plasma concentrations of LCM at steady state.

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
- Serious adverse events (SAEs)

2.2.1.2 Other safety variables

The other safety variables include:

- Laboratory tests (hematology, clinical chemistry, and urinalysis parameters)
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (ie, blood pressure and pulse rate)
- Body weight

2.2.2 Pharmacokinetic/Pharmacodynamic variable

The pharmacokinetic (PK) variable is the following:

- Plasma concentrations of LCM versus time postdose.

2.2.3 Efficacy variables

Efficacy evaluations will be based on subject diaries where seizure types, dates, and number of seizures are recorded. The exploratory efficacy variables are:

- Proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) during the Monotherapy Period.
- Proportion of subjects remaining seizure free for 12 consecutive months (52 consecutive weeks) during the Monotherapy Period.
- Time to discontinuation is evaluated as time to withdrawal of treatment due to AE or lack of efficacy (LOE) in the Monotherapy Period.

2.3 Study design and conduct

EP0057 is a Phase 3, multicenter, open-label, study designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as monotherapy at doses from 200mg/day to 600mg/day in Japanese adults with partial-onset seizures with or without secondary generalization who are not controlled by monotherapy with an AED with marketing approval in Japan.

The duration of the study per subject is up to 2.5 years, including a 1-week Screening Period and an approximately 2.5-year Treatment Period.

A Screening Visit (Visit 1) is conducted to evaluate subject suitability for enrollment. This visit can be conducted on more than 1 day but not more than 7 days. Subjects who fulfill all eligibility criteria shall be enrolled.

At the beginning of the 4-week Titration Period, subjects will start with LCM 100mg/day. The dose is increased by 100mg/day each week until the 400mg/day dose is reached at the beginning of Week 4. Subjects who are unable to tolerate LCM during the Titration Period will be withdrawn from the study.

During the AED Withdrawal Period, concomitant AEDs will be carefully tapered and discontinued within 4 to 12 weeks. To improve tolerability and reduce drug load, tapering of the concomitant AED may be started during the Titration Period. For safety reasons, tapering of the concomitant AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

Subjects who complete the AED Withdrawal Period will enter the Evaluation Period. The Evaluation Period lasts for 52 week and followed by a long term Follow-Up Period. The Follow-Up Period will continue until LCM is available on the market as monotherapy in Japan. Both the Evaluation Period and the Follow-Up Period are collectively termed as the Monotherapy Period.

During the AED Withdrawal and Monotherapy Period, the investigator may increase or decrease the dose of LCM to optimize tolerability and seizure control. The LCM dose may be decreased no lower than 200mg/day or increased, no faster than 100mg/day per week, up to 600mg/day.

For subjects receiving LCM at a dose less than 600mg/day at the beginning of the Monotherapy Period who experience a new seizure (first seizure during the Monotherapy Period), the LCM dose will be increased up to 600mg/day by a maximum increment of 100mg/day weekly.

Subjects who are continuing in the Follow-Up Period until LCM is commercially available as monotherapy will complete the End-of-Study Visit assessments. Subjects who prematurely withdraw from the study at any time during the study will complete the Early Withdrawal Visit assessments. All subjects who enter the Monotherapy Period and prematurely terminate the study will enter a Taper Period. During the Taper Period, subjects receiving doses greater than LCM 200mg/day at the Early Withdrawal Visit/End-of-Study Visit should be tapered off gradually at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that a more rapid withdrawal of LCM is required due to safety concerns. UCB (or designee) should be contacted if a more rapid withdrawal is required. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. Subjects receiving doses of LCM 200mg/day or lower at the Early Withdrawal Visit/End-of-Study Visit are not required to taper off LCM. A Final Visit will be required 2 weeks after the last LCM dose is administered. Subjects who continue in the Monotherapy Period until LCM is commercially available as monotherapy in Japan, and decide to continue on commercial LCM are not required to enter the Taper Period; the End-of-Study Visit will be the last visit for these subjects. If LCM is not commercially available in Japan at the time the study closes, access to LCM will be provided according to the laws.

2.4 Determination of sample size

No formal sample size calculation has been performed. A minimum of 10 subjects are anticipated to participate in this study within the enrollment period from Jan 2014 to Jan 2015.

2.5 Schedule of study assessments

The schedule of study assessments is provided in Table 2-1.

Table 2–1: Schedule of study assessments

	Screening Period	Titration Period (4 wk)		AED Withdrawal Period (4 to 12 wk)		Monotherapy Period						Taper Period		
						Evaluation (52 wk)					Follow Up			
Visit	**1**	**2**	**3**	**4**	**5, 6[a]**	**MPV 1[b]**	**MPV 2**	**MPV 3**	**MPV 4**	**MPV ≥5**	**ESV[c] /EWV[c]**	**ETV**	**Final Visit[d]**	**Unscheduled Visit[e]**
Visit window (days)	±3	-	±3	±7	±7	±14	±14	±14	±14	±14	-	-	-	-
Informed consent	X													
Demographic and epilepsy information	X													
Inclusion/ exclusion criteria	X	X												
Concomitant AED	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/ procedure history	X													
Complete physical	X					X				X[f]	X			

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						Evaluation (52 wk)					Follow Up			
Visit	**1**	**2**	**3**	**4**	**5, 6[a]**	**MPV 1[b]**	**MPV 2**	**MPV 3**	**MPV 4**	**MPV ≥5**	**ESV[c] /EWV[c]**	**ETV**	**Final Visit[d]**	**Unscheduled Visit[e]**
examination														
Brief physical examination				X				X		X[f]				X
Vital signs (BP, PR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[g]	X			X		X		X		X	X			X
Complete neurological examination	X					X				X[h]	X			
Brief neurological examination				X				X		X[h]				X
EEG[i]	X													
MRI/CTi	X													
ECG (12-lead)[j]	X		X	X		X		X		X	X		X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X		X	X	X	X	X	X	X	X	X		X	X
Pregnancy test[k]	X		X	X	X	X	X	X	X	X	X		X	X
CM plasma			X	X	X	X	X	X	X	X	X			X

Table 2–1: Schedule of study assessments

	Screening Period	Titration Period (4 wk)		AED Withdrawal Period (4 to 12 wk)		Monotherapy Period						Taper Period		
						Evaluation (52 wk)				Follow Up				
Visit	**1**	**2**	**3**	**4**	**5, 6[a]**	**MPV 1[b]**	**MPV 2**	**MPV 3**	**MPV 4**	**MPV ≥5**	**ESV[c] /EWV[c]**	**ETV**	**Final Visit[d]**	**Unscheduled Visit[e]**
concentration														
Registration	X	X												
Dispense IMP		X	X	X	X	X	X	X	X	X	X[1]			X
IMP return/review			X	X	X	X	X	X	X	X	X	X		X
Dispense subject diary	X	X	X	X	X	X	X	X	X	X	X[1]	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X	X	X	X	X
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; ECG=electrocardiogram; EEG=electroencephalogram; ESV=End-of-Study Visit; ETV=End-of-Taper Visit; EWV=Early Withdrawal Visit; IMP= investigational medicinal product; LCM=lacosamide; MPV=Monotherapy Period Visit; MRI=magnetic resonance imaging; PR=pulse rate; wk=weeks

[a] At the beginning of AED Withdrawal Period, the baseline AED will be carefully tapered and discontinued within a period of 4 to 12 weeks. For safety reasons, tapering of the baseline AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

[b] MPVs will be performed at 13-week intervals.

[c] At the time of study completion, or if subjects discontinue the study prematurely, an ESV/EWV will be performed. The ESV is the last visit for subjects who choose to continue on to commercial LCM treatment. Subjects receiving doses greater than LCM 200mg/day at the ESV/EWV should be tapered off gradually at a recommended rate of LCM 200mg/day per week, unless a more rapid withdrawal of LCM due to safety concerns is required. The sponsor should be contacted if the more rapid withdrawal is required. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary.

[d] A Final Visit will be, completed 2 weeks after the last dose of LCM.

[e] The investigator may use an Unscheduled Visit to increase LCM dose if a new seizure occurs, to adjust a subject's LCM dose, to repeat laboratory tests or ECG findings, to follow up on AEs. Additional assessments can be completed as needed at the investigator's discretion.

[f] The complete physical examination will be performed every 52 weeks after MPV 5. The brief physical examination will be performed every 52 weeks after MPV 3.

[g] Height will be recorded at Visit 1 only.

[h] The complete neurological examination will be performed every 52 weeks after MPV 5. The brief neurological examination will be performed every 52 weeks after MPV 3.

[i] Required on Visit 1 if no previous EEG and/or CT/MRI has been performed during the last 24 months prior to Visit 1.

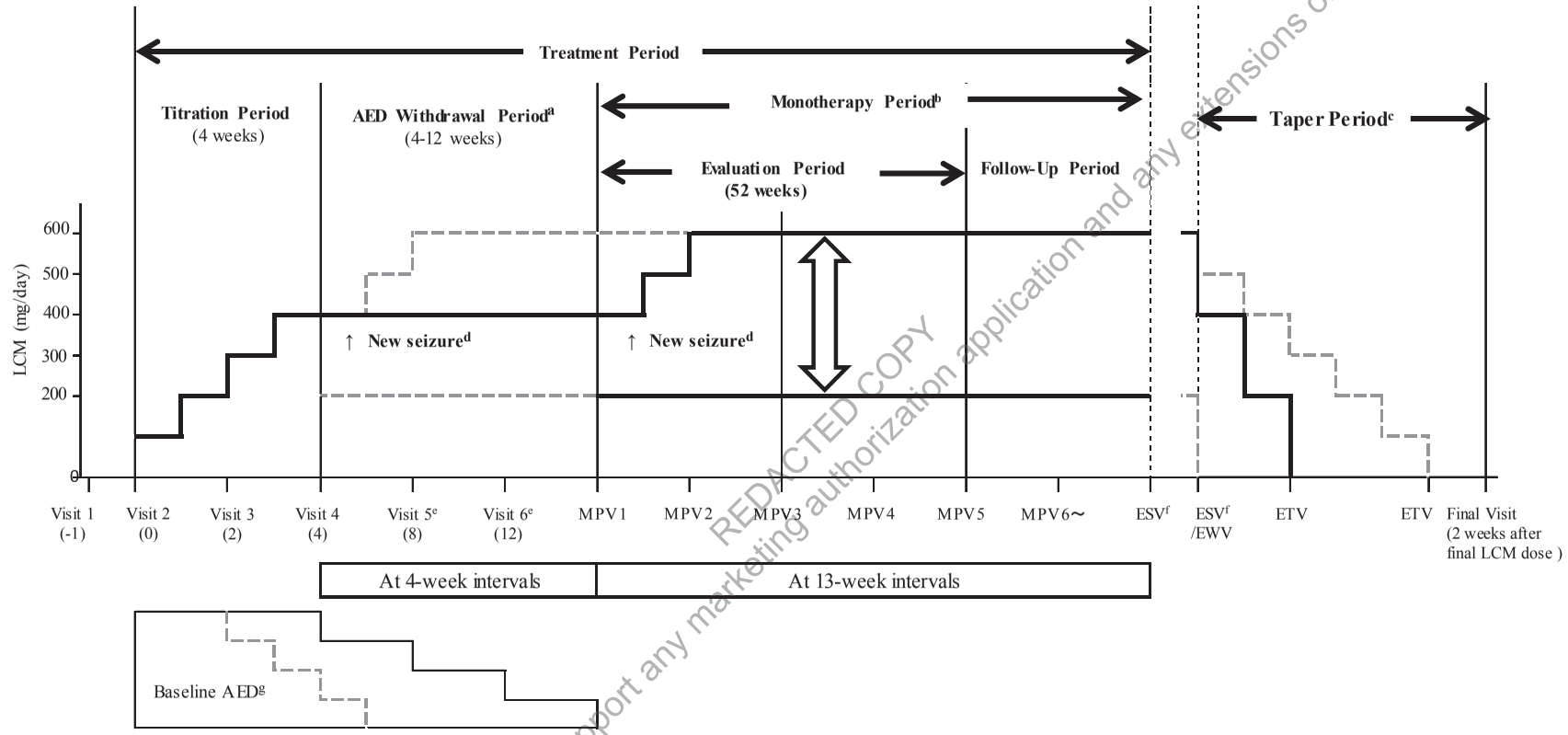
[j] Electrocardiogram (12-lead) examination will be performed Visit 1, Visit 3, Visit 4, and MPV 1, MPV 3, MPV 5 and every 26 weeks after MPV 5, and at the ESV/EWV. If an ECG abnormality is detected at the EWV, an ECG will be performed in the following visit of the Taper Period for safety follow up. If an ECG abnormality is found at the ESV, it will be followed up by postmarketing surveillance.

[k] A serum pregnancy test will be performed at Visit 1. A urine pregnancy test will be performed at each visit where the laboratory assessments are performed.

[l] At ESV, IMP and subject diary will not be dispensed for subjects who complete the Monotherapy Period and choose to continue on to commercial LCM treatment.

2.6 Schematic diagram

Figure 2–1: Schematic diagram



( )= weeks; AED=antiepileptic drug; ESV= End-of-Study Visit; ETV= End-of-Taper Visit; EWV= Early Withdrawal Visit; LCM=lacosaminde; MPV= Monotherapy Period Visit

[a] At the beginning of the AED Withdrawal Period, the baseline AED will be carefully tapered and discontinued during a period of a maximum of 12 weeks. For safety reasons, tapering of the baseline AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

[b] In the LCM Monotherapy Period, a flexible dose ranging between 200 and 600mg/day will be used depending on the conditions of individual subjects. During this period, visits will be performed at 13-week intervals.

[c] Subjects receiving doses greater than LCM 200mg/day at the ESV/EWV 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. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. Subjects receiving LCM 200mg/day at the ESV/EWV are not required to taper off LCM.

[d] When the subjects receiving LCM at a dose less than 600mg/day at the beginning of the Monotherapy Period/AED Withdrawal Period have a new seizure during the Monotherapy Period/AED Withdrawal Period, the LCM dose will be increased up to 600mg/day. In other cases, the investigator will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure control. The LCM dose may be decreased to a minimum dose of 200mg/day or increased to a maximum dose of 600mg/day in weekly steps of no faster than 100mg/day per week.

[e] During the AED Withdrawal Period, if the concomitant AED withdrawal is reached at the 4th week after Visit 4, Visit 5 and Visit 6 will be canceled. If the concomitant AED is withdrawn within 8 weeks, Visit 6 will be canceled.

[f] The ESV is the last visit for subjects who complete the Monotherapy Period and choose to continue taking commercial LCM. Subjects who complete the Monotherapy Period and choose not to continue taking commercial LCM will complete the ESV and enter a Taper Period.

[g] To improve tolerability and reduce drug load, tapering of the baseline AED may be started during the Titration Period. For safety reasons, tapering of the baseline AED will be at the discretion of the investigator, and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

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 9.2 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%.

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 be use 1 additional decimal place compared to the original data.
- Minimum and maximum will have the same number of decimal places as the original value.

A complete set of data listings containing documented data and calculated data (eg, change from Baseline) will be generated.

For plasma concentrations, no summary table of descriptive statistics will be presented due to the small number of subjects. Only subject listings will be generated.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day

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

3.2.1.2 Relative day from the start date of Monotherapy

Relative day from the start date of Monotherapy will be calculated as the current date minus the date of first dose in Monotherapy Period plus 1 for days on or after the day of first dose in Monotherapy Period and prior to or on the day of last dose in the Monotherapy Period (eg, the day of first dose in Monotherapy Period will be Day 1). Relative day from the start date of Monotherapy will be calculated as date of first dose in Monotherapy Period minus the current

date for days prior to the first dose in Monotherapy Period (the day prior to first dose in Monotherapy Period will be Day -1). For days after the last dose in Monotherapy Period, relative day from the start date of Monotherapy will be calculated as the current date minus the date of last dose in Monotherapy Period including a "+" to denote post Monotherapy treatment days (eg, the day after the last dose in Monotherapy Period will be Day +1). Relative day from the start date of Monotherapy will not be calculated for partial dates.

3.2.1.3 End date of the Treatment Period

The end date of the Treatment Period will be either the date of End-of-Study Visit (ESV) for the subjects continuing the study until LCM is available on the market as monotherapy in Japan, or the date of Early Withdrawal Visit (EWV) for the subjects who prematurely withdraw from the study. For the subjects who enter the Monotherapy Period, the end date of the Treatment Period is equal to the end date of Monotherapy Period. If a subject does not have an ESV/EWV, then either the date of the last scheduled or unscheduled visit during the Treatment Period will define the end date of the Treatment period.

3.2.2 Study periods

The following study periods are defined for the classification by study periods:

3.2.2.1 Screening Period

Screening Period: the Screening Visit (Visit 1) date to the day prior to the day of first dose of study drug at Visit 2. The Screening Period can last more than 1 day but no more than 7 days.

3.2.2.2 Treatment Period

The Treatment Period consists of the Titration Period, the AED Withdrawal Period, and the Monotherapy Period.

3.2.2.2.1 Titration Period

Titration Period: Visit 2 date (the date of first dose of study drug) to the day prior to Visit 4 date, or to the EWV date if a subject discontinued during the Titration Period, even though withdrawal of Baseline AED could have been started during this period. This will be a 4-week forced titration period and the dose of LCM will start from 100mg/day and increase to 400mg/day at the end of the Titration Period.

3.2.2.2.2 AED Withdrawal Period

AED Withdrawal Period: Visit 4 date to the day prior to the Monotherapy Period Visit 1 (MPV1) date, or the EWV date if a subject discontinued during the AED Withdrawal Period. This will be up to a maximum of 12-week period including Visit 4, Visit 5, and Visit 6, in which the Baseline AED will be carefully tapered and discontinued. Visit 5 and Visit 6 can be skipped if withdrawal of Baseline AED has been reached within 4 weeks after Visit 4 (both Visit 5 and Visit 6 can be skipped) or within 8 weeks after Visit 4 (Visit 6 can be skipped). The AED withdrawal Period will not be defined for a subject if withdrawal of Baseline AED has been started and completed during the Titration Period.

3.2.2.2.3 Monotherapy Period

The Monotherapy Period consists of the 52-week Evaluation Period (MPV1 to MPV4) and the Follow-up Period (subsequent visits after MPV4).

Evaluation Period: MPV1 date to the day prior to MPV5 date, or to the EWV date if a subject discontinued during the Evaluation Period.

Follow-up Period: MPV5 date to ESV date, or to the EWV date if a subject discontinued during the Follow-up Period.

3.2.2.2.4 Taper Period

The Taper Period includes an End of Taper Visit (ETV) and a Final Visit. The Taper Period will start from the day after the ESV for a patient who chooses not to continue on commercial LCM treatment or from the day after the EWV if a patient enters the EWV to the Final Visit date. The ETV can be skipped if the subjects receiving LCM 200mg/day or lower at the ESV/EWV as tapering off of LCM is not required for such cases.

For subjects who continue to receive commercial LCM after the ESV, the Taper Period will not be performed.

3.2.3 Mapping of assessments performed at Early Withdrawal Visit

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

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

3.2.4 Mapping of assessments performed at Unscheduled Visit

Efficacy and safety assessments at an Unscheduled Visit will not be mapped to any Scheduled Visit. They will be considered to use for determining the last, minimum, and maximum post-Baseline value during the Treatment Period.

3.2.5 Subjects who Completed the Study

This study will continue until the date of market approval of LCM for the monotherapy indication in Japan, otherwise until the development of LCM for the partial-onset seizure monotherapy indication is discontinued. The subjects who could continue the Monotherapy Period until the date of market approval of LCM for the monotherapy indication in Japan are defined as subjects who completed the study. “Subject status at study termination” in the Study Termination CRF is completed for all completed subjects.

3.3 Definition of Baseline values

In general, Baseline values for safety variables will be based on the last non-missing data collected prior to the first dose of LCM, unless otherwise noted for a specific type of data.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on the interpretation of the study data. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined separately in the Specification of Protocol Deviations (SPD) document. To the extent feasible, rules for identifying important 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, the protocol deviations will be considered according to the following categories:

- Inclusion criteria deviation
- Exclusion criteria deviation
- Withdrawal criteria deviation
- Prohibited concomitant medication use
- Incorrect treatment or dose
- Treatment non-compliance
- Procedural non-compliance

Important protocol deviations will be reviewed prior to database snapshot/lock.

3.5 Analysis sets

Safety and PK variables will be summarized using the Safety Set (SS), and efficacy variables will be summarized using Full Analysis Set (FAS).

3.5.1 Safety Set

The SS will consist of all enrolled subjects who have received at least 1 dose of study medication.

3.5.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of subjects in the SS who have been having at least 1 seizure diary assessment.

3.6 Treatment assignment and treatment groups

All eligible subjects will receive LCM and dose will be optimized during the Treatment Period according to the tolerability and seizure control. In terms of presentation of summary tables, all subjects will be summarized together across all dose levels. For adverse events, subject listings will be displayed with dose level at onset.

3.7 Center pooling strategy

All analyses are presented pooled for all centers. No by-center analysis is planned as the total number of subjects is small.

3.8 Coding dictionaries

Medical history and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL) version Sep 2013. Medical Procedures will not be coded.

3.9 Changes to protocol-defined analyses

NA

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No adjustment for covariates is planned for this study.

4.2 Handling of dropouts or missing data

Subjects who prematurely withdraw from the study will be evaluated based on the data collected at each visit attended.

Subjects who complete the study or who prematurely withdraw from the study not due to AEs nor LOE, will be censored as of the last dose of LCM in the time to withdrawal due to AEs or LOE analysis.

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

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

- If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the trial termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the trial termination CRF.
- If a subject died and has a partial or missing last administration date, the date is to set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.
- If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact according to the study termination CRF. A review of the data for subjects with completely missing last dose dates should be performed to ensure that the imputation does not result in a unrealistic value for duration of exposure.

Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the CRF should be presented in subject data listings (no imputed dates should be included in subject data listings. Partial data information for dates of AEs and concomitant medications will be imputed to determine whether they are treatment emergent or concomitant. Likewise, partial data information for dates of Diagnosis of Epilepsy will be imputed in order to calculate the duration of epilepsy at study entry. Details are described in each section.

AEs with missing intensity and/or missing relationship to LCM will be considered as ones with the highest intensity and/or having relationship in the summary.

No other imputation of missing values is planned for the safety and efficacy analyses unless specified otherwise.

4.3 Interim analyses and data monitoring

No official interim analysis and data monitoring, which are organized for any decision making on the study conduct, are planned for this study. However database will be snapshot and data analysis will be performed for the purpose of new drug application (NDA) submission after all subjects completed 26 weeks of treatment. Interim data reports for the purpose of regulatory submission are planned for this study before the final analysis.

4.4 Multicenter studies

No by-center analysis is planned for this study.

4.5 Multiple comparisons/multiplicity

Not applicable.

4.6 Use of an efficacy subset of subjects

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

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

In order to investigate the impact of the following characteristics on efficacy, subgroup analysis will be performed on the efficacy endpoint, proportion of subjects remaining seizure free for 6 consecutive months during the Monotherapy Period. (Section 8.1.4.2).

- Gender (male, female)
- Use of CBZ as Core AED at study entry (yes, no)
- ILAE seizure classification history (1A, 1B, 1C)
- Modal dosage during Monotherapy Period (>400mg/day, =<400mg/day)

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Reasons for screen failures will be summarized for all the subjects screened. The number and percentage of subjects screened, and the number and percentage of screen failures by the reason and overall will be presented.

Disposition of subjects screened will be summarized for all the subjects screened. The number of subjects in SS, and FAS, dates of first subject in and out, and number of subjects screened will be presented by investigator site and overall. Number of sites, number of principal investigators, and principal investigator name at each site will also be displayed.

Disposition and discontinuation reasons will be summarized for the SS by Treatment Periods and overall. The number and percentage of subjects who completed/ongoing/discontinued the study and primary reason for discontinuation will be displayed. This would be further divided to subjects who completed/ongoing/discontinued the Treatment Period and the reason for

discontinuation, who completed/ongoing/discontinued the Titration Period and the reason for discontinuation, who completed/ongoing/discontinued the AED Withdrawal Period and the reason for discontinuation, who completed/ongoing/discontinued the Monotherapy Period and the reason for discontinuation, who completed/ongoing/discontinued the Evaluation Period and the reason for discontinuation, who completed/ongoing/discontinued the Follow-up Period and the reason for discontinuation, who completed/ongoing/discontinued the Taper Period and the reason for discontinuation. The number and percentage of subjects who continuing commercially available LCM, and who entering the Taper Period will be displayed for overall the study.

A list of subject disposition will be created for all the subjects screened. Site and subject number, subject status, date of informed consent, dates of first and last study medication, duration in days of study medication, date and the primary reason for discontinuation, and date of a final contact will be presented.

A list of subject analysis sets will be created for all the subjects screened. Site/subject number, yes/no for each analysis sets, and the reasons of excluded from the analysis sets will be displayed.

A list of study discontinuation will be created with site/subject number, the primary reason for discontinuation, period, LCM dose at one day before the discontinuation date, and relative days for the SS.

A list of subjects who did not meet study eligibility criteria will be created for all the subjects screened.

A list of visit dates will be created for all the subjects screened.

5.2 Protocol deviations

Important protocol deviations will be evaluated prior to database snapshot/lock.

A list of important protocol deviation will be created for the SS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics and other baseline characteristics will be summarized and listed.

6.1 Demographics

Demographic variables will be summarized for the SS. The demographic variables to be summarized are:

- Age (years): continuous and categorized as (<=18, >18->65, >=65)
- Gender
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m2)
- Ethnicity
- Racial Group (Asian, Other)

– Racial Subgroup

Demographic variables will be listed for all subjects in the SS.

6.2 Other Baseline characteristics

6.2.1 Baseline epilepsy characteristics

Baseline epilepsy characteristics will be summarized for the SS.

A table of Diagnosis of Epilepsy will be created. The followings will be summarized.

– Age at diagnosis (years)

  Derived using the epilepsy diagnosis date and the date of birth. Imputation methods should be applied for missing or partial epilepsy diagnosis date. 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, or the subject's birthdate. If only a year is available, the later of the following dates will be imputed: January 1st of the year, or the subject's birthdate. If both month and year are missing, no imputation will be done.

– Duration of epilepsy at study entry (years)

  Derived as (the date of informed consent – the date of epilepsy diagnosis)/365.25.

  Imputation for partial dates of epilepsy diagnosis should be imputed as described above for the age at diagnosis.

A table of Baseline AED will be created. The following s will be summarized.

– Number of Lifetime AEDs
– Use of CBZ as Core AED at study entry (yes, no)

A table of Etiology of Epilepsy will be created. A frequency distribution will be displayed for the following.

– Etiology Unknown
– Etiology Known

In the cases of Etiology is unknown, further classification will be summarized:

– Idiopathic
– Cryptogenic

In the cases of Etiology is known, further classification will be summarized (a subject can appear in more than 1 category):

– Genetic origin
– Congenital, total and in categories defined in CRF.
– Perinatal events, total and in categories defined in CRF
– Cranial trauma
– Cerebral neoplasm

- Brain surgery
- Primary degenerative lesion
- Cerebrovascular accident
- Cerebral infection
- Toxic cause
- Metabolic cause
- Other

A table of International League Against Epilepsy (ILAE) Seizure Classification History will be created. A frequency distribution will be displayed for the following. A subject can appear in more than 1 category.

- Partial onset seizures, total and in categories defined in CRF
- Generalized seizures, total and in categories defined in CRF
- Unclassified epileptic seizures

A table of Focus Localization will be created. A frequency distribution will be displayed for the followings. A subject can appear in more than 1 category.

- Frontal
- Temporal
- Parietal
- Occipital
- Unknown

A table of Classification of Epileptic Syndromes will be created. A frequency distribution will be displayed for the followings. A subject can appear in only 1 category.

- Localization related, total and in categories defined in CRF.
- Generalized
- Epilepsies and syndromes undetermined whether focal or generalized, total and in categories defined in CRF
- Special syndromes

A table of Baseline EEG and Baseline CT/MRI will be created. A frequency distribution will be displayed for the categories defined in CRF.

Subject Listings of all Baseline epilepsy characteristics will be created for the SS. Specification of "other" will be displayed in the listings.

6.2.2 Childbearing Potential

A list of females with child bearing potential will be created for females in the SS.

6.3 Medical history and concomitant diseases

Medical history will be summarized by MedDRA system organ class (SOC) and Preferred Term (PT) for the SS. Number and percentage of subjects with history will be displayed in each system. All tabulations will be sorted by alphabetical SOC, descending frequency of PT within SOC.

Concomitant diseases will be summarized in a similar way. Concomitant diseases are defined as medical history events that are ongoing at Visit 1.

Medical history and concomitant diseases will be listed in the subject listing. A glossary of MedDRA terms and associated investigator's terms for medical history will also be presented.

Procedure history will also be listed in the subject listing for the SS.

6.4 Prior and concomitant medications

Medication will be summarized using Anatomical Therapeutic Chemical (ATC) codes from the WHO-DRL dictionary for the SS. All tabulations will be sorted by frequency of the highest level ATC code and by frequency of the lower level ATC code within the highest level ATC code.

Prior medications are medications that started prior to the date of first dose of study drug. Concomitant medications are medications taken at least one day in common with the study drug dosing period. Prior and concomitant medications will be reported on the Prior and Concomitant Medications CRF page. Additionally, lifetime use of Antiepileptic drugs (AEDs) will be reported on the Prior Medications Historical of AED CRF page. All AEDs used as regular and/or rescue will be reviewed prior to database snapshot/lock.

Medication with partial start date and/or partial end date will be imputed according to the rules defined as follows in order to determine if it is a prior medication or a concomitant medication.

Imputation of Partial Start Dates

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

Imputation of Partial Stop Dates

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

AEDs will be summarized separately from the other medications (non-AEDs) for the SS. Prior and concomitant AEDs used regularly during the Treatment Period will be presented by 4-level ATC (5-digit) terms and preferred medication name.

Prior and concomitant non-AEDs will be summarized separately by 1-level and 2-level ATC (3-digit) terms, which will include any medications used as rescue for seizure.

Lifetime, prior and concomitant medications of AEDs, and prior and concomitant medication of non-AEDs will be listed separately for the SS. The reasons for discontinuation of lifetime AEDs will also be displayed in the lifetime AEDs listing. A glossary of ATC codes and associated investigator's terms for all medications will also be listed with Core AED flag.

Concomitant medical procedure will also be listed for the SS.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment Compliance will not be assessed due to the flexible dosing of study drug. A subject list of study medication administration will be created for the SS. Daily Dose with the start date and the end date, Dose Level at the start date of the Daily Dose, Study Period during the start date and the end date of the Daily Dose will be listed.

8 EFFICACY ANALYSES

The primary objective of this study is to evaluate the long-term safety and tolerability of LCM and the efficacy analysis is planned as an exploratory one, so no primary efficacy variables are defined in this study.

All efficacy analyses will be based on the FAS unless specified otherwise.

8.1 Analysis of efficacy variable(s)

Efficacy evaluations will be based on the subject diaries where seizure types, dates, and number of seizures are recorded. The exploratory efficacy variables are:

- Proportion of subjects remaining seizure free for 6 consecutive months during the Monotherapy Period.
- Proportion of subjects remaining seizure free for 12 consecutive months during the Monotherapy Period.
- Time to discontinuation is evaluated as time to withdrawal of treatment due to AE or lack of efficacy (LOE) in the Monotherapy Period.

8.1.1 Proportion of subjects remaining seizure free for 6 consecutive months during the Monotherapy Period

A day with seizure data missing (ie, "Not Done" is noted on the Seizure Count CRF) will be considered as a day with no seizure in the efficacy analyses unless otherwise specified. A subject will be considered as seizure free if no seizure is reported during a period time.

Number and percentage of subjects achieving a seizure free status for 6 consecutive months (182 days) from the day of MPV1 in the Monotherapy Period, and the 2-sided 95% confidence interval (CI) according to the exact method will be calculated and displayed. Evaluation of 6-month seizure free status should be limited to subjects exposed to study medication for at least 6

months and having Seizure Diary Information at least 6 months. Subjects who discontinue the study before the end date of 6 consecutive months will not be included in the analysis.

8.1.2 Proportion of subjects remaining seizure free for 12 consecutive months during the Monotherapy Period

The same methods described in Section 8.1.1 will be applied for the subjects achieving a seizure free status for 12 consecutive months (364 days) from the day of MPV1 in the Monotherapy Period.

8.1.3 Time to discontinuation due to AE or lack of efficacy (LOE) in the Monotherapy Period

Time to discontinuation due to AE or LOE in the Monotherapy Period from the first study medication dose date during the Monotherapy Period will be estimated with Kaplan-Meier methods.

The event is defined as discontinuation due to AE or LOE in the Monotherapy Period. Otherwise discontinuation due to the other reason in Monotherapy Period will be handled as censored. The end of Study Visit will also be handled as censored for the subjects completed.

Time to the event / censored for each subject will be defined as days from Date of the first administration of LCM during the Monotherapy Period until Date of the event / censored, calculated as (the date of event / censor – the date of the first dose of study medication during the Monotherapy Period +1). Subject who discontinued before Monotherapy Period will not be included in this analysis.

A Kaplan-Meier Plot will be created. Median survival time will be provided in days.

8.1.4 Other efficacy analysis

8.1.4.1 Maximum duration of consecutive seizure free days

The maximum duration of consecutive seizure free days in the Monotherapy Period and the Evaluation Period for each subject will be summarized. The maximum duration of consecutive seizure free days will be listed in a subject listing.

8.1.4.2 Time course change in LCM dose and seizure frequency per 28 days

By subject figures of time course change of LCM dose (mg/day) and seizure frequency per 28 days will be created for overall of the study. Visit number at X-axis, LCM dose (mg/day) and seizure frequency per 28 days at Y-axis will be displayed. LCM dose (mg/day) at a particular visit will be plotted by line plot, and seizure frequency per 28 days during a particular visit interval will be shown by bar chart, respectively. Here, seizure frequency per 28 days at a particular visit will be calculated as:

Seizure frequency per 28days at a particular visit: = (Number of seizure during the previous visit to the visit) x (28 / days during the previous visit to the visit).

The relative day, the relative day from the start date of Monotherapy, and the seizure frequency per 28 days will be displayed at each visit. Seizure count will be listed in subject listings. Time to discontinuation due to AE or LOE in Monotherapy will be listed in subject listings with the Dose level of LCM at the event occurred.

8.1.4.3 Subgroup analysis

In order to investigate the impact of the important characteristics on efficacy, the primary efficacy analysis described in Section 8.1.1 will be repeated by gender (male, female), by usage of CBZ as Core AED at study entry (yes, no), by ILAE seizure classification history (1A, 1B, 1C), and by Modal dosage during Monotherapy Period (>400mg/day, =<400mg/day). Here, for the subgroup analysis by ILAE seizure classification history, only the same type of seizure with historical type will be considered for seizure free status, i.e., for analysis with subgroup of 1A type seizure, number and percentage of subjects achieving a seizure free only for 1A type seizure will be calculated.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics analysis will be performed on the SS.

9.1 Pharmacokinetics

LCM plasma concentrations will be listed in the subject listing for the SS. Period, visit, date, relative days, relative days from the Monotherapy Visit, dose level, actual amount of last dose, date and time of last dose, actual time, and LCM plasma concentrations will be displayed. Here, actual amount of last dose is defined as:

- Daily dose at one day before the plasma sampling date, if sampling is conducted before the morning dose.
- Sum of Last Dose Amount corrected in CRF and a half of daily dose at one day before the plasma sampling date, if sampling is conducted before the evening dose.

10 SAFETY ANALYSES

The primary objective of this study is to evaluate the long-term safety and tolerability of LCM, and primary safety variables of AEs, subject withdrawals due to AEs, and SAEs are defined.

All safety analyses will be performed on the SS.

10.1 Extent of exposure

The number of days of exposure during the Treatment Period is calculated as (the date of final dose within Treatment Period – the date of the first dose of study medication + 1). Days with unknown or zero doses that are prior to the date of last dose are included in the calculation. Study medication duration (days) will be summarized using descriptive statistics by Period and overall. Subject-years of exposure in the study is calculated as the total LCM exposure across all subjects divided by 365.25. It will be calculated by Period and overall.

The maximum daily dose (mg/day) is defined as the highest total daily dose a subject received during the study. The total daily dose will be reported on the Drug Dosing Log CRF page. The modal dose (mg/day) is defined as the daily dose the subject received for the longest duration during the study. For any calculated modal dose falling between 2 consecutive modal dose categories should be presented with the category reflecting the lower dose. If a subject was on two different doses for the same number of days in the study, the modal dose will be assigned as the lower of the two doses. Gaps in dosing (ie., days with zero dosing or no dosing information) will be excluded from the calculation of the modal dose.

The maximum dose and the modal dose are presented in 100mg/day categories (eg., 100mg/day, 200mg/day, 300mg/day, etc.) by period and overall.
Extent of exposure will be listed. Study medication duration (days), the maximum daily dose (mg/day), and the modal dose (mg/day) will be displayed.

10.2 Adverse events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as AEs that started on or after the date of first dose of study medication and within 30 days following the date of last study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose. If the date of the last dose of study medication is unknown, and AEs occurring or whose intensity worsened after the first dose of study medication will be considered treatment-emergent. Pre-treatment AEs are AEs with start dates prior to the first dose of study medication. It will be recorded for all subjects screened.

Missing dates of onset of AEs are imputed according to the rules as follows in order to determine if it is treatment-emergent or not.

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

TEAEs will be assigned to Titration Period, AED Withdrawal Period, Monotherapy Period, and Taper Period based on the AE onset dates or the intensity worsened dates. If the dates are missing, the same rules as above will be applied for assignment of Treatment Periods. AEs will be tabulated by MeDRA SOC and MedDRA PT. The number and percentage of subjects experiencing each event at least once will be summarized. Number of individual AE occurrences will be also presented in selected tables. All summaries will be sorted alphabetically by SOC and by frequency of events within SOC.

The following summaries will be presented for the AEs:

- An overview summary of AEs will be presented. It will include the numbers and percentages of subjects with at least one TEAEs, at least one serious TEAEs, at least one TEAEs leading to discontinuation, at least one drug-related TEAEs, at least one severe TEAEs, and death.
- An overview summary of the AEs by Periods will be presented in a similar way as above.
- Incidence of TEAEs will be presented by Period, and overall.
- Incidence of TEAEs by Maximum Intensity will be presented by Period and overall.

- Incidence of TEAEs by Maximum Relationship will be presented by Period and overall.
- Incidence of Treatment-Emergent Serious AEs will be presented by Period and overall.
- Incidence of TEAEs Leading to Study Discontinuation will be presented by Period and overall.
- Incidence of other significant TEAEs will be presented by Period and overall.

Individual subject data listings will be presented for all AEs, serious AEs, AEs leading to death, AEs leading to discontinuation, and other significant TEAEs which are defined by the MedDRA term in Appendix 13.1. Dose level of study drug at onset and the Period at onset will be displayed. A glossary of MedDRA terms and associated investigator's terms will also be presented.

10.3 Clinical laboratory evaluations

For continuous laboratory variables of hematology, chemistry, descriptive statistics of actual value and change from Baseline will be presented by visit. In addition, descriptive statistics of the actual value and change from Baseline will be presented for the last, minimum, and maximum post-Baseline value obtained during the Treatment Period. Repeated or unscheduled laboratory assessments during the study will not be used in by-visit summary, but will be considered when determining the last, minimum, and maximum post-Baseline values during Treatment Period. The number and percentage of subjects with treatment-emergent marked laboratory abnormalities (TEMA) for hematology and chemistry as defined in Appendix 13.2 will be summarized by period (Titration Period, AED Withdrawal Period, Monotherapy Period, and Taper Period) and overall. Treatment-emergent is defined meeting the criteria at any post-Baseline visit during the Treatment Period and not meeting the same criteria during the Screening Period. Addition to the parameters listed in Appendix 13.2, the combination of total bilirubin ≥2 x ULN and ALT ≥3 x ULN, and the combination of total bilirubin ≥2 x ULN and AST ≥3 x ULN will also be presented in the summary. Subject numbers for those meeting the treatment-emergent marked abnormality criteria will also be presented.

Actual value and change from Baseline of all laboratory parameters (hematology, chemistry, and urinalysis) will be listed with their abnormalities in the subject data listing. TEMA hematology and chemistry values will be flagged in the listings.

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

10.4.1 Vital signs and body weight

Descriptive statistics of the actual value and change from Baseline for vital signs and body weight will be presented by visit. In addition, descriptive statistics of the actual value and change from Baseline will be presented for the last, minimum, and maximum post-Baseline value obtained during the Treatment Period. Repeated or unscheduled assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last, minimum, and maximum post-Baseline value during the Treatment Period.

The number and percentage of subjects with abnormal will be presented by visit.

Actual value and change from baseline of all vital signs and body weight will be listed with their abnormalities in the subject data listing.

The abnormal criteria are defined as follows:

Table 10–1: Vital sign assessments – abnormal

Vital Sign	Abnormality Criteria
Systolic Blood Pressure (mmHg)	≥180 and increase of ≥20 from baseline ≤90 and decrease of ≥20 from baseline
Diastolic Blood Pressure (mmHg)	≥105 and increase of ≥15 from baseline ≤50 and decrease of ≥15 from baseline
Pulse Rate (bpm)	≥120 and increase of ≥15 from baseline ≤50 and decrease of ≥15 from baseline
Body weight	≥ 10% change from Baseline (an increase or a decrease)

10.4.2 Electrocardiograms

For all quantitative ECG measurements (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT intervals using Bazett and Fridericia corrections), descriptive statistics of the actual values and change from Baseline will be presented by visit. In addition, descriptive statistics of the actual value and change from Baseline will be presented for the last, minimum, and maximum post-Baseline value obtained during the Treatment Period. Repeated or unscheduled assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last, minimum, and maximum post-Baseline value during the Treatment Period.

The Bazett corrected QT (QTcB) will be calculated as:

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

The Fridericia corrected QT (QTcF) will be calculated as:

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

The number and percentage of subjects with classified QT intervals as <450ms, 450 to <480ms, 480 to <500ms, ≥500ms in actual values, and <30ms, 30 to <60ms, and ≥60ms in increase from Baseline will be summarized by visit.

The number and percentage of subjects with ≥500ms in actual value, with ≥60ms increase from Baseline, and with ≥500ms in actual value or ≥60ms increase from Baseline on the maximum post-Baseline value of QT intervals obtained during the Treatment Period will be summarized.

The number and percentage of subjects with treatment-emergent values of PR interval, with treatment-emergent values of QRS intervals and with abnormal values of heart rate will be summarized by Treatment Period and overall in Treatment Period.

Actual value and change from Baseline will be listed in the subject listing. Abnormal value will be marked in the listing.

The criteria of abnormalities are defined as follows:

Table 10–2: Electrocardiogram (ECG) – abnormal

Parameter	Abnormality Criteria
QT interval (ms)	≥500, or ≥60 increase from Baseline
QTcB interval (ms)	≥500, or ≥60 increase from Baseline
QTcF interval (ms)	≥500, or ≥60 increase from Baseline
PR interval (ms)	Treatment-emergent value >200, >220, >250
QRS interval (ms)	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	<50, >120

ECG interpretation and ECG findings will be provided by site investigator and the central vendor. Number and percentage of subjects with any ECG finding will be summarized by each finding

and any findings. In this summary, number of subjects who will have their 12-lead ECG Baseline and after the first administration of LCM, and not have the finding at Baseline will be used as the denominator. Number and percentage of subjects in each category of ECG interpretation will be summarized by visit. ECG finding by the central vendor and ECG interpretation by site investigator will be listed in the subject listing.

10.4.3 Physical and neurological examinations

Physical examination findings will be listed in the subject data listings.

Abnormal neurological examination will be listed by subject.

10.4.4 Assessment of suicidality

The Columbia-Suicide Severity Rating Scale (C-SSRS) assessment results will be listed by subject.

10.4.5 Assessment of pregnancy

Urine pregnancy test assessment results will be listed by subject.

11 OTHER ANALYSES

11.1 Drug Accountability

Drug accountability will be listed for the SS.

12 REFERENCES

Not applicable.

13 APPENDICES

13.1 Other significant AEs

Table 13–1: Other significant AEs

MedDRA Preferred Term
HEPATOTOXICITY RELATED TERMS
Hepatitis toxic
Hepatotoxicity
CARDIAC AND ECG RELATED TERMS
Atrioventricular black 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 behavior
Suicidal ideation
Suicide attempt
Intentional self-injury
Self-injurious behavior
Self-injurious ideation
Intentional overdose
Poisoning deliberate
ADDITIONAL TERMS

Table 13–1: Other significant AEs

MedDRA Preferred Term
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 Laboratory assessments – Marked Abnormalities (MA)

The following criteria will be applied in the determination of marked abnormalities for laboratory assessment values.

13.2.1 Hematology

Table 13–2: Hematology

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional unit)*	*Unit (standard)*	*Abnormality Criteria (standard unit)*	*Comment/rationale*
Hematocrit	<2y	%	≤27 >45	%	≤27 >45	Based on clinical relevance
	2y - <17y		≤29 >47		≤29 >47	Based on clinical relevance
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN	Based on clinical relevance
Hemoglobin	<2y	g/dL	≤9.0 >15.0	g/L	≤90 >150	Approximately 1/3 HCT
	2y - <17y		≤9.5 >16.0		≤95 >160	Approximately 1/3 HCT
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN	Approximately 1/3 HCT
WBC/Leukocytes	All	10^9/L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0	Based on clinical relevance; Applied from adult LCM MA criteria
Lymphocytes Absolute	<2y	10^9/L	<1.0 >9.8	G/L	<1.0 >9.8	derived from adult MA criteria:~ 40% below LLN & 25% above ULN

Table 13–2: Hematology

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional unit)*	*Unit (standard)*	*Abnormality Criteria (standard unit)*	*Comment/rationale*
	2y - <6y		<0.7 >6.9		<0.7 >6.9	derived from adult MA criteria:~ 40% below LLN & 25% above ULN
	≥6y		<0.6 >5.0		<0.6 >5.0	derived from adult MA criteria:~ 40% below LLN & 25% above ULN
Basophils	>1m	%	≥5.0	%	≥5.0	Based on clinical relevance; applied from adult LCM MA criteria
Basophils Absolute	>1m	10^9/L	≥0.4	G/L	≥0.4	Based on clinical relevance; applied from adult LCM MA criteria
Eosinophils	>1m	%	≥10	%	≥10	applied from adult LCM MA criteria
Eosinophils Absolute	>1m	10^9/L	≥1.0	G/L	≥1.0	applied from adult LCM MA criteria
Monocytes	>1m	%	≥20.0	%	≥20.0	applied from adult LCM MA criteria
Monocytes Absolute	>1m	10^9/L	≥2.0	G/L	≥2.0	applied from adult LCM MA criteria
Neutrophils Absolute	>1m	10^9/L	<1.5	G/L	<1.5	Based on clinical relevance; ANC to be defined only for MA criteria; Applied from LCM MA criteria
Platelets	>1m	10^9/L	≤100 ≥600	G/L	≤100 ≥600	Applied from adult LCM MA criteria
Platelets	<2y	10^{12}/L	<3.0	T/L	<3.0	Based on clinical relevance
RBC/ Erythrocytes	≥2y		<3.5		<3.5	Based on clinical relevance

Abbreviations: ANC = absolute neutrophil count; m = month, y = year. A month is defined as 30 days; a year is defined as 365.25 days.

13.2.2 Chemistry

Table 13–3: Chemistry

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional)*	*Unit (standard)*	*Abnormality Criteria (standard)*	*Comment/rationale*
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	carried over from LCM MA & PCST
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	carried over from LCM MA & PCST
Alkaline Phosphatase	<4y	U/L	≥690	U/L	≥690	Applied from PCST value based on clinical relevance
	4y - <10y		≥834		≥834	Applied from PCST value based on clinical relevance
	10y - <17y		≥1761		≥1761	≥3X ULN, applied from LCM MA criteria
	≥17y		≥3.0 x ULN		≥3.0 x ULN	≥3X ULN, applied from LCM MA criteria
GGT	<6m	U/L	≥522	U/L	≥522	>3X ULN, applied from LCM MA criteria
	6m - <1y		≥279		≥279	>3X ULN, applied from LCM MA criteria
	1y - <13y		≥66		≥66	>3X ULN, applied from LCM MA criteria
	13y - <17y		≥126		≥126	>3X ULN, applied from LCM MA criteria
	≥17y		≥3.0 x ULN		≥3.0 x ULN	>3X ULN, applied from LCM MA criteria
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208	applied from LCM MA criteria

Table 13–3: Chemistry

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional)*	*Unit (standard)*	*Abnormality Criteria (standard)*	*Comment/rationale*
Total Protein	2m-<1y	g/dL	<3.0 >11.9	g/L	<30 >119	0.75X below LLN, 1.5X ULN
	1y - <17y		<4.3 >12.0		<43 >120	0.75X below LLN, 1.5X ULN
	≥18y		<4.3 >13.0		<43 >130	0.75X below LLN, 1.5X ULN
Albumin	<1y	g/dL	<1.6 >7.2	g/L	<16 >72	0.75X below LLN, 1.5X ULN
	≥1y - <17y		<2.4 >8.4		<24 >84	0.75X below LLN, 1.5X ULN
	≥17y		<2.6		<26	0.75X below LLN, 1.5X ULN
BUN	<1y	mg/dL	≥24	mmol/L	≥8.568	20x the value for Cr
	1y - <17y		≥36		≥12.852	20x the value for Cr
	≥17y		≥40		≥14.28	20x the value for Cr
Urea	<1y	mg/dL	>42	mmol/L	>7.014	Applied from PCST value
	≥1y		>60		>10.02	Applied from PCST value
Creatinine	1y - <10y	mg/dL	>1.2	umol/L	>106.8	Clinical relevance
	10y - <16y		>1.8		>159.12	Clinical relevance
	≥16y		≥2.0		≥176.8	Applied from LCM MA criteria
Creatinine Clearance*	All	mL/min	<50	mL/s	<0.835	Clinical relevance

Table 13–3: Chemistry

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional)*	*Unit (standard)*	*Abnormality Criteria (standard)*	*Comment/rationale*
Bicarbonate	>1m - <17y	mEq/L	<15 >38	mmol/L	<15 >38	Clinical relevance
	≥17y		<18 >38		<18 >38	Clinical relevance
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05	Applied from PCST value based on clinical relevance
	1y - <17y		<7.4 >11.7		<1.85 >2.925	Applied from PCST value based on clinical relevance
	≥17y		≤7.6 ≥11.0		≤1.9 ≥2.75	Soldin et al. +/- 1 mg/dL of reference interval
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112	Applied from LCM MA criteria
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486	Applied from PCST value based on clinical relevance
	1y - <17y		<1.8 >7.4		<0.5814 >2.3902	Applied from PCST value based on clinical relevance
	≥17y		≤2.0 ≥6.0		≤0.646 ≥1.938	Soldin et al. +/- 1 mg/dL of reference interval
Potassium	<1y	mEq/L	≤3.0 ≥6.5	mmol/L	≤3.0 ≥6.5	-.2, +.4mEq/L, Applied from 2006 PCST criteria
	≥1y		≤3.0 ≥6.0		≤3.0 ≥6.0	Applied from LCM MA criteria

Table 13–3: Chemistry

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional)*	*Unit (standard)*	*Abnormality Criteria (standard)*	*Comment/rationale*
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151	Applied from LCM MA criteria
Glucose	>1m - <17y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99	Applied from 2006 PCST criteria, clinical relevance
	≥17y		<50 ≥200		<2.775 ≥11.1	Clinical relevance
Total Cholesterol	≥1y	mg/dL	>250	mmol/L	>6.475	Applied from LCM MA criteria
LDL (calculated)	1y - <17y	mg/dL	>140	mmol/L	>3.626	+10 mg/dL ULN
	≥18y		>200		>5.18	+10 mg/dL ULN
HDL	≤2y	mg/dL	<10	mmol/L	<0.259	approx. 20% less than lower limit
	>2y		<20		<0.518	approx. 20% less than lower limit
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475	1.5X ULN
	≥1y		>300		>3.39	1.5X ULN
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996	+ 1mg/dL LN
	1y - <13y		>6.5		>386.62	+ 1mg/dL LN
	13y - <17y		>8.6		>511.528	+ 1mg/dL LN
	≥17y		>9.5		>565.06	Applied from LCM MA criteria
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264	-1, +2 below/above limit of normal; clinical relevance
	≥1y		≤3.8		≤48.9098	carry over from adult MA criteria

Table 13–3: Chemistry

Parameter	*Age Range*	*UNIT (conventional)*	*abnormality Criteria (conventional)*	*Unit (standard)*	*Abnormality Criteria (standard)*	*Comment/rationale*
			≥13.5		≥173.7585	
Globulin	<1y	g/dL	<1.0 >4.5	g/L	<10 >45	0.75X below LLN, 1.5X ULN
	≥1y		<1.2 >5.3		<12 >53	0.75X below LLN, 1.5X ULN

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

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

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

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

Once the Statistical Analysis Plan was approved, all amendments were defined in this section.

14.1 AMENDMENT 1

After the review of Dry TFLs at the 1st Dry Run, the following amendments were made. Amendment points other than typo or any other miss wording are described here.

Modifications and changes

Specific changes

- Section 2.4 Determination of sample size

Actual status of subject number of entry, and entry period are added.

- Section 3.2.1.3 Endo date of the Treatment Period

In order to correct a miss wording, terms of "for the subjects who enter the Monotherapy Period" are added.

- Section 3.2.5 Subjects who Completed the Study

In order to clarify how to know the subject status of completion, a sentence is added as "Subject status at study termination" in Study Termination CRF is completed for all completed subjects.

- Section 3.2.6 Days of 6 months and 12 months

This definition is only for the efficacy, so delete the section.

- Section 3.3 Definition of Baseline values

Delete the terms of "efficacy" as baseline is defined only for safety valuables in this study.

- Section 4.2 Handling of dropouts or missing data

Imputation method for partial date or missing date is added according to UCB global convention.

- Section 4.3 Interim analyses and data monitoring

Clarify the timing and objective of interim analysis.

- Section 4.8 Examination of subgroups

Subgroup analysis is change to be required. Subgroup factors are described.

- Section 5.1 Subject disposition

Number of sites and number of principal investigators are added in a disposition of subject screen table.

Disposition and discontinuation reasons table is required for Taper Period.

LCM dose at one day before the discontinuation date is used alternatively in study discontinuation listing.

- Section 6.2.1 Baseline epilepsy characteristics

A table of baseline AED is added, and Number of Lifetime AEDs and Use of CBZ as Core AED at study entry (yes, no) are displayed in it.

- Section 6.4 Prior and concomitant medications

Imputation method for partial end date is added.

Summary table of Life time AED is deleted.

Clarify rescue medications for seizure is included in non-AED summary.

Core AED flag is added in a glossary of ATC codes and associated investigator's term listing.

- Section 7 Measurement of treatment compliance

Variables to be listed in study medication administration are clarified.

- Section 8.1.3 Time to discontinuation due to AE or lack of efficacy (LOE) in the Monotherapy Period

Analysis population is clarified as subjects who discontinued before Monotherapy Period will not be included in this analysis.

- Section 8.1.4 Other efficacy analysis

Divide three subsections, 8.1.4.1 is for Maximum duration of consecutive seizure free days, 8.1.4.2 is for Time course change in LCM dose and seizure frequency per 28 days, and 8.1.4.3 is added for Subgroup analysis.

- Section 8.1.4.2 Time course change in LCM dose and seizure frequency per 28 days

Seizure frequency per 28 days is added as 2nd Y axis.

- Section 8.1.4.3 Subgroup analysis

Subgroup analysis is added. The primary efficacy analysis will be repeated by subgroups.

- Section 9.1 Pharmacokinetics

Add a definition of actual amount of last dose to be listed.

- Section 10.1 Extent of exposure

Analysis variables are clarified as study medication duration and subject-year exposure.

A summary of subject number and percentage in treatment duration categories is deleted.

Maximum dose and modal dose are summarized by period and overall.

- Section 10.2 Adverse events

Incidence of TEAEs will be summarized not only overall but also by Period.

Incidence of TEAEs by Maximum Intensity, Incidence of TEAEs by Maximum Relationship, Incidence of TESAEs, Incidence of TEAEs Leading to Study Discontinuation, and Incidence of other significant TEAEs are added by Period and overall.

- Section 10.3 Clinical laboratory evaluations

Taper Period is added to TEMA by period summary.

- Section 10.4.2 Electrocardiograms

Summary of treatment-emergent values should be summarized not by visit, but by Treatment Period, so it is updated.

How to summarize ECG interpretation and ECG finding is collected.

- Section 13.1 Other significant AEs

Table is updated based on the preferred term at MedDRA 16.1.

14.2 AMENDMENT 2

After the DEM3 conducted on 01 April 2016, the following amendments were made. Amendment points are described here.

Modifications and changes

- Section 8.1.1 Proportion of subjects remaining seizure free for 6 consecutive months during the Monotherapy Period

The following underlined words were insert in order avoid to misunderstanding.

Evaluation of 6-month seizure free status should be limited to subjects exposed to study medication for at least 6 months and having Seizure Diary Information at least 6 months.

- Section 10.4.2 Electrocardiograms

The following underlined words were insert in order avoid to misunderstanding.

ECG interpretation and ECG findings will be provided by site investigator and the central vendor. Number and percentage of subjects with any ECG finding will be summarized by each finding and any findings. In this summary, number of subjects who will have their 12-lead ECG Baseline and after the first administration of LCM, and not have the finding at Baseline will be used as the denominator. Number and percentage of subjects in each category of ECG interpretation will be summarized by visit. ECG finding by the central vendor and ECG interpretation by site investigator will be listed in the subject listing.

- Section 13.2.2, Table 13-3 Chemistry

The abnormal criteria of AST, ALT were added according to the UCB global convention.