STATISTICAL ANALYSIS PLAN

Study: EP0012

Product: Lacosamide

AN OPEN-LABEL, MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY FOR UNCONTROLLED PRIMARY GENERALIZED TONIC-CLONIC SEIZURES IN SUBJECTS WITH IDIOPATHIC GENERALIZED EPILEPSY

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018
SAP Amendment #2	10 Oct 2019
SAP Amendment #3	15 Nov 2021
SAP Amendment #4	09 Sep 2022

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
bid	twice a day
BMI	body mass index
BRI	Behavioral Regulation index
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool version
B	Baseline
CB	Combined Baseline Period
CBCL	Child Behavior Checklist
COVID-19	Coronavirus disease 2019
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DBP	diastolic blood pressure
ECG	Electrocardiogram
ES	Enrolled Set
ET	Early Termination
EQ-5D-3L	3-Level EuroQol-5 Dimension Quality of Life Assessment
FAS	Full Analysis Set
GEC	Global Executive Composite
GGT	Gamma glutamyl transferase
HRQoL	health-related quality of life
IGE	idiopathic generalized epilepsy
II	Generalized seizures
IIA	Absence seizure
IIB	Myoclonic seizure
IIE	Primary generalized tonic-clonic seizure
ILAE	International League Against Epilepsy

IPD	Important protocol deviations
LCM	Lacosamide
LLN	lower limit of normal
MA	Markedly abnormal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Metacognition Index
NCI CTC	National Cancer Institute common toxicity criteria
PB	Prospective Baseline Period
PCH	percent change
PedsQL	Pediatric Quality of Life Inventory
PGTCS	primary generalized tonic-clonic seizures
PT	preferred term
QOLIE-31-P	Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31
QTcB	Bazett corrected QT
QTcF	Fridericia corrected QT
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	statistical analysis software
SBP	systolic blood pressure
SD	standard deviation
SF	seizure frequency
SOC	system organ class
SPD	Specification of protocol deviations
SS	Safety Set
TEAE	treatment emergent adverse event
TEMA	treatment emergent markedly abnormal
ULN	upper limit of normal
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol number EP0012, through protocol amendment #5; the data summarized will be from EP0012 unless otherwise stated. Since EP0012 is an open-label extension of SP0982, the SP0982 SAP Amendment #4 should be consulted for how variables were calculated for the randomized subjects rolling into EP0012.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to assess the safety and tolerability of lacosamide (LCM) as an adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures (PGTCS) in subjects with idiopathic generalized epilepsy (IGE) during long-term exposure.

2.1.2 Secondary objectives

The secondary objectives are:

- To assess the efficacy of adjunctive LCM therapy during long-term exposure for the treatment of subjects with IGE experiencing uncontrolled PGTCS
- To allow subjects who have completed SP0982 and eligible Baseline failures from SP0982 to receive LCM

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

The primary safety variables are:

- The incidence of TEAEs over the duration of the Treatment Period
- Subject withdrawals due to TEAEs
- Incidence of new appearance of absence and/or myoclonic seizures during the Treatment Period
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days during the Treatment Period as compared to the Prospective Baseline Period
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days during the Treatment Period as compared to the Prospective Baseline Period
- At least 50% worsening in days with absence seizures
- At least 50% worsening in days with myoclonic seizures

2.2.1.2 Secondary safety variables

Secondary safety variables are:

- Percentage of treatment-emergent marked abnormalities in hematology and chemistry parameters
- Percent of treatment-emergent marked abnormalities in 12-lead electrocardiogram (ECG)
- Percentage of treatment-emergent marked abnormalities in vital sign measurements (ie, blood pressure (BP) and pulse rate)

2.2.1.3 Other safety variables

Other safety variables are:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-Lead ECGs
- Changes in vital sign measurements (ie. BP and pulse rate), including weight and height and physical (including neurological) examination findings
- Achenbach Child Behavior Checklist (CBCL)1½-5 or CBCL/6-18 (for pediatric subjects only)
- Cognitive function assessment Behavior Rating Inventory of Executive Function (BRIEF)/BRIEF-P (for pediatric subjects only)

2.2.2 Efficacy variables

2.2.2.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

2.2.2.2 Secondary efficacy variable

The secondary efficacy variable is:

- Percent change in PGTCS frequency per 28 days from Combined Baseline Period, where Combined Baseline Period is defined as the combined 12-week Historical Baseline and 4-week Prospective Baseline periods immediately prior to randomization in the parent study (SP0982)

2.2.2.3 Other efficacy variables

The other efficacy variables are:

- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period
- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period
- At least a 50% reduction in PGTCS frequency compared to the Combined Baseline Period

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

2.2.2.4 Additional other efficacy variables

Additional other efficacy variables that will be analyzed in this SAP are:

- Change in days with generalized seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with generalized seizures per 28 days relative to the Prospective Baseline Period
- Change in days with all seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with all seizures per 28 days relative to the Prospective Baseline Period
- At least a 50% reduction in generalized seizure days compared to the Prospective Baseline Period
- At least a 50% reduction in all seizure days compared to the Prospective Baseline Period
- Seizure-free status (yes/no) for all seizure types
- Duration of PGTCS free intervals
- Duration of all generalized seizure-free intervals

- Duration of all seizure-free intervals

2.3 Study design and conduct

This is a multicenter, open-label extension study to assess the long-term safety, tolerability and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTCS (seizure type=IIE) in subjects ≥4 years of age with IGE. This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 study (or have left the primary study at the time of the 125th event, whichever came first) as well as eligible Baseline failures from SP0982. Then, some subjects who tapered in SP0982 after the 125th event may enter EP0012 for the Safety Follow-up only (ICF to be signed beforehand). Up to 250 subjects from 150 to 180 study sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, study completers from SP0982 who are eligible for inclusion in EP0012, SP0982 Safety Follow-up subjects, and Others are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTCS criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTCS during that time or
- Subjects who experience a second PGTCS after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTCS within the 24-week Treatment Period of SP0982
- Subjects who were ongoing in SP0982 when the 125th event occurred

SP0982 Safety Follow-Up subjects

- Subjects tapered in SP0982 after the 125th event occurs will enter EP0012 for the Safety Follow-Up only; these subjects take no study medication in EP0012 and their EP0012 reason for discontinuation is that they are completing SP0982 Follow-up in EP0012.

Other

- Subjects that enrolled in EP0012 that did not fall into the above categories, like those who were incomplete screeners

For SP0982 subjects consented under SP0982 Protocol Amendment 5, after the 125th event is confirmed, two classes of SP0982 subjects will be allowed to enroll in EP0012. Subjects who are being screened in SP0982, at the time of the 125th event, will be allowed to directly enroll into EP0012, thus their screening and baseline data will be captured in SP0982 but some of their baseline data may be captured in EP0012; their treatment information will be captured in EP0012. For subjects who are concluding their SP0982 LCM treatment and tapering, these

SP0982 participants will be consented to enroll in EP0012 and complete their Safety Follow-Up (thus not receiving any LCM) in EP0012; the data captured in EP0012 will not be transferred to SP0982.

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures and incomplete screeners from SP0982 who choose to enter this study will undergo a complete Visit 1.

For adult subjects, treatment will continue for at least 2 years. Once 2 years of participation are reached, adult subjects will continue to participate until 1 of the 2 following conditions are met:

- LCM is approved for use for the treatment of PGTCS in subjects with IGE in the subject's country or
- until the latest approval is granted either by EMA, FDA or PMDA.

For pediatric subjects, treatment will continue until 1 of the following 2 conditions are met:

- up to 5 years of participation or
- until the approval of the extension of indication to cover the target age group is granted.

Adult and pediatric subjects are completers if they continue in the study for the maximum duration in their respective region.

The following study periods for the EP0012 protocol (not for the analysis) are defined:

- A Treatment Period lasting at least 2 years for adults enrolled into EP0012 (may be shorter for adults leaving the study when the PGTCS indication approvals are obtained during the course of the study).
- A Treatment Period lasting at least 5 years (238 weeks) for the population less than 18 years old at enrollment in EP0012 (may be shorter as some participants leave the study when the PGTCS indication approvals are obtained during the course of the study).
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator and do not have to perform the tapering (Taper Visit and SFU).
  - Subjects tapering off LCM will do so over a period of up to 4 weeks.
  - An End of Taper Visit (latest 3 days after the final dose) will occur after the final LCM dose for subjects who taper off LCM. Following the End of Taper Visit, there will be a 30-day Safety Follow-Up Period. The Safety Follow-Up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-Up telephone contact 30 days after the last dose of study drug. The same design will apply to some of the subjects tapered in SP0982 at the time of the 125th event and who entered EP0012 for the Safety Follow-Up Visit only and to subjects who entered EP0012 for a Safety Follow-Up Visit after discontinuing SP0982 due to the study stopping.

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

Subjects who entered EP0012 as <18 years and become adults (18 years and older) during the study will remain in the study for at least 5 years (238 weeks).

2.3.1 EP0012 entry status

Subjects who enter EP0012 are either rollovers from SP0982 or direct enrollers in EP0012.

2.3.1.1 Rollover subjects

The subjects enrolled in EP0012 who were randomized in SP0982 and entered EP0012 after discontinuation or completion of SP0982. All study data captured in EP0012 prior to the Safety Follow-up period will be summarized as on-treatment (or during the treatment period) for these subjects, even if the procedure was done before the 1st dose of EP0012 study medication.

2.3.1.2 Direct enrollers

The subjects enrolled in EP0012 who were baseline failures or incomplete screeners in SP0982 who were never randomized to take SP0982 study medication.

2.3.2 Protocol visit windows

Protocol visit windows are ±7 days.

2.4 Determination of sample size

The sample size of this open-label extension study will be determined by the parent SP0982 study. SP0982 is an event-driven study. Up to 250 subjects may be enrolled to meet the required number of events. Baseline failures from SP0982, subjects in screening at the end of SP0982 and SP0982 subjects completing their Safety follow-up in EP0012 will also be eligible for EP0012, which may increase the sample size.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

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

All appropriate tables, figures and listings will present the study results by All Subjects, Pediatrics (>=4 to <18 years old in EP0012), and Adults (>=18 years old in EP0012). Study results for assessments given only to pediatric subjects will present information by All Subjects. A pediatric subject is less than 18 years old at EP0012 Visit 1.

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 with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum; for some parameters, Q1 and Q3 may also be displayed.

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

- "n" will be an integer.
- Mean, SD, and median will use 1 additional decimal place compared to the original data.
- Minimum, Q1, Q3 and maximum will have the same number of decimal places as the original value.

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

Efficacy analyses will be performed on data reported during the analysis Treatment Period (see Section 3.2.1.1) on the Full Analysis Set (FAS). PGTCS analyses will be done on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 consecutive days, any PGTCS reported during the gap will not be included in PGTCS summaries.

Safety analyses (which include analyses on absence (seizure type=IIA) and/or myoclonic seizures (seizure type=IIB)) will be performed on data reported during the analysis Treatment Period for the Safety Set (SS).

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Analysis periods

The following analysis periods are defined:

- Treatment Period (this analysis Treatment Period differs from the protocol-defined treatment period): The Treatment Period, which will apply to all non-efficacy analyses, starts at the time of first dose of study medication during the EP0012 study for the direct enrollers (date of first visit for rollover subjects) and ends on the date of last dose of study medication or the date of last protocol-defined visit before SFU visit or death date, whichever is later. The Treatment Period includes the protocol-defined Taper Period (see Section 3.2.2) if the subject completes it.
  - An efficacy analysis Treatment Period must be calculated for the PGTCS-related analyses. This time period starts at the time of first dose of study medication during the EP0012 study (date of first visit for rollover subjects) and ends on the date of last dose of study medication or death date, whichever is later.
- Post-Treatment Period: The Post-Treatment Period is defined as the treatment free (ie, no study medication) observational phase after the Treatment Period (in SP0982 or EP0012) where study is taken. It starts on the day after the end date of the Treatment Period and ends on the date of the final visit or date of last contact with the subject, whichever is later. For the subjects from SP0982 who are completing their Safety Follow-up in EP0012, their entire time in EP0012 will be deemed to be in the Post-Treatment Period due to the subjects not taking study medication in EP0012.

If the date of last dose of study medication is missing, see imputation rules in Section 4.2.4.

3.2.1.2 Relative day

Relative day will be calculated as the current date minus the date of first dose of study medication in EP0012 for direct enrollers (first visit date for rollover subjects) plus 1 for days on or after the day of first dose of study medication and prior to or on the day of last study medication dose (eg, the day of first dose or first visit will be Day 1). Relative day will be calculated as date of first dose of study medication for direct enrollers or first visit for rollovers in EP0012 minus the current date for days prior to the first dose of study medication (the day prior to first dose or first visit will be Day -1). For days after the last dose of study medication, relative day will be calculated as the current date minus the date of last dose of study medication including a "+" to denote post treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

3.2.1.3 Last Visit

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

3.2.1.4 Month

A month is defined as 28 days.

3.2.1.5 Completer cohorts

A completer cohort will be defined as the subset of subjects in the FAS that were enrolled, treated with LCM for the specified duration of time (allowing gaps of 3 days or less), and have efficacy data available for the duration of the treatment exposure stated in the name of the cohort minus the visit window (7 days). For example, a 22-week completer cohort consists of subjects from the FAS, treated with LCM for at least 22 weeks minus 7 days and have efficacy data through at least 22 weeks minus 7 days of exposure (Visit 5 or ET visit).

Subjects will be classified as belonging to one or more of the following completer cohorts for the purpose of subgroup analyses:

- 22 weeks
- 46 weeks
- 94 weeks.
- 142 Weeks
- 190 Weeks
- 238 Weeks

3.2.1.5.1 Use of ET or Termination Visit when Scheduled Visits are missing

A subject is considered a completer of EP0012 if Visit 11 (Week 94 = 658 days minus 7 days) or ET or Termination visit is completed instead of Visit 11 . Visit 11 or Week 94 was chosen as the visit where subjects could complete the study because it was the closest visit occurring to 2 years given the 6 month visit schedule. Subjects also may be deemed completers of EP0012 when they leave the study due to LCM being approved in their region.

If the visit that corresponds to the completer cohort is missing, then ET or Termination visit will be checked to see if this data can be used for the missing visit and to complete the data needed for the completer cohort.

For assessing the 22 and 46 Week completer cohorts, respectively, assess whether the ET visit was completed instead of Visit 5 (minus 7 days) or Visit 8 (minus 7 days), respectively; the Termination visit may not be an option for some subjects for the 22 Week or 46 Week Completer cohorts since subjects can only complete the study after 2 years or approval in their region.

Since subjects can complete EP0012 at Week 94 (minus 7 days) for the 94 Week completer cohort (and for later completer cohorts), if the Week 94 (Visit 11) is missing, then assess whether the Termination or ET visit was completed instead of Visit 11.

The assessment of using Termination or ET visit to determine whether a subject completes a cohort occurs when the subject is missing visit for XX Week Completer Cohort (Week 22 – Visit 5(minus 7 days), Week 46 – Visit 8 (minus 7 days), Week 94 – Visit 11 (minus 7 days), Week 142 – Visit 13 (minus 7 days), Week 190 - Visit 15 (minus 7 days), and Week 238 – Visit 17 (minus 7 days)) and there are no other later protocol-scheduled visits indicating the subject was exposed longer in the study. Review the Protocol's Schedule of Study Assessments to determine the number of weeks (and calculate the expected date) from the prior visit that the Termination or ET visit is expected. The Termination or ET visit must not be any more than 7 days earlier than expected date for XX Week Completer Cohort, as protocol visit windows are ±7 days; if the ET or Termination visit date is too early, the subject did not complete enough exposure to be included in XX Week Completer Cohort.

Subjects in the completer cohort may have their data further presented by smaller time periods within the duration of the completer cohort as presented in Section 3.2.1.6. When a subject qualifies for a particular completer cohort, the subject has data for the entire completer cohort; this means that the subject has data for the smaller time periods within the completer cohort.

3.2.1.6 Time Period

Some time period labels are used for completer cohort tables as well as non-completer cohort tables. When the tables present time periods within a completer cohort, the subject, by definition, has data for the entire time period whereas for the non-completer cohort tables, the subject may not have data for the entire time period.

The time periods for the Treatment Period seizure analysis are "0 to 22 Weeks", ">22 to 46 Weeks", ">46 to 94 Weeks", ">94 to 142 Weeks", ">142 to 190 Weeks", ">190 to 238 Weeks", "0 to 46 Weeks", "0 to 46 Weeks (> 22 Weeks)", "0 to 94 Weeks", "0 to 94 Weeks (> 46 Weeks)", "0 to 142 Weeks", "0 to 142 Weeks (>94 Weeks)", "0 to 190 Weeks", "0 to 238 Weeks" and entire "Treatment Period". Additional time periods will be added based on the visit schedule as subjects progress through the study. All tables displaying Time Period should show all time periods.

The time periods for the Treatment Period include all data in the time window of the time period of interest including termination, early termination and end of taper visit data, taking into account the 7 day visit window. A calculation will be needed using dates to determine what time period the termination, early termination and end of taper visit data fit into for each subject, adjusting for the 7 day visit window. While completer cohorts and their time periods involve

subjects having data for the entire cohort or time period, when it comes to non-completer cohort tables, subjects may not have data for the whole Treatment period or time period within the Treatment period.

For example, for non-completer cohort tables, "0 to 46 Weeks" contains all data from all subjects in 0-46 weeks, where Week 46 is Visit 8, if present; if a subject discontinues the study at Visit 4, the subject is still summarized in "0 to 46 Weeks". "0 to 46 Weeks (>22 Weeks)" contains all data for all subjects who have data through at least Visit 5 (Week 22). If a subject only has data up to Week 14 (Visit 4), the subject will appear in "0 to 46 Weeks" but not in "0 to 46 Weeks (>22 Weeks)".

3.2.1.7 Visit Algorithm

In determining the date of visits, which is specifically helpful in determining whether patients are members of completer cohorts, the in-clinic date of the visit will be used instead of visit dates from SDTM.SV (the Study Visits SDTM dataset which contain in-clinic and non-clinic visit dates). In-clinic visit dates, firstly from SDTM.VS (Vital Signs), will be used as the date of protocol-specified visits. If a visit is missing in SDTM.VS, then the in-clinic visit date from SDTM.DA (Drug Accountability) will be used as the date of the protocol-specified visit. If a visit is missing in SDTM.VS and SDTM.DA, then the in-clinic visit date from SDTM.LB (Laboratory Results) will be used as the data of the protocol-specified visit.

3.2.2 Protocol defined study periods

The following study periods are defined in the protocol:

- Treatment Period: at least a 2-year period following enrollment. The Treatment Period starts on the date of Visit 1 and continues until the date of the ET Visit or Termination Visit.
- Taper Period: up to 4-week period following the Treatment Period for subjects who discontinue from the study at any time. The Taper Period starts the day after the Treatment Period ends and continues until the date of last dose of study medication or the End of Taper Visit.
- Safety Follow-up Period: 30-day period following the Taper Period. The Safety Follow-up Period starts the day after the last dose of study medication or End of Taper Visit and continues until the Safety Follow-up telephone contact date.

3.2.3 Seizure cluster

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

3.2.4 AEDs and benzodiazepines

Antiepileptic drugs (AEDs) and benzodiazepines will be collected on the concomitant and prior medication case report form (CRF) for AEDs. New concomitant AEDs can be added at any time. Benzodiazepines are AEDs. The UCB study physician will review a listing of all medications and flag which ones are to be summarized as AEDs and benzodiazepines since AEDs may be entered on the wrong medication case report form.

Concomitant AEDs at SP0982 entry, concomitant benzodiazepine use at SP0982 entry, and Lifetime AEDs and Benzodiazepines for the rollover subjects are already calculated and carried forward into EP0012.

For EP0012 direct enrollers, concomitant AEDs at study entry are defined as AEDs where the start date is on or before 28 days prior to EP0012 Visit 1 and the medication was still ongoing on the date of Visit 1. The concomitant AEDs for the rollover and direct enroller subjects will be presented as Concomitant AEDs at the start of study medication dosing.

Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to EP0012 (direct enrollers) Visit 1; ongoing AEDs are not counted as a lifetime AED. The lifetime AEDs for direct enrollers and rollover subjects will be presented as Lifetime AEDs and Benzodiazepines prior to start of study medication dosing

Concomitant benzodiazepine use at EP0012 entry is the use of any benzodiazepine at EP0012 Visit 1. The concomitant benzodiazepine use for direct enrollers and rollover subjects will be presented as Concomitant benzodiazepine use at the start of study medication dosing.

Stable use of benzodiazepines is allowed as concomitant AEDs. Intermittent use of benzodiazepines is allowed as rescue medication for epilepsy indications with a maximum of 1 dose per week. Benzodiazepines used as rescue medication will be flagged with "RESCUE" in the indication field on the CRF. Rescue AEDs will also be identified programmatically as any AED with an epilepsy or seizure related indication taken for 1 or 2 days, at any frequency.

If a subject is unable to take study medication, commercial lacosamide can be taken instead in order to fill the gaps in exposure. In this instance, the commercial lacosamide usage is considered a substitute for study medication in determining whether a subject has > 3 day LCM gap and counting PGTCS occurring in such a gap; no exposure records will be created to add commercial lacosamide to study medication exposure. The start and end date of commercial LCM usage will be calculated and stored in ADSL for use in PGTCS analyses.

The preferred term reported on the concomitant medication CRF is lacosamide.

3.2.4.1 Phenytoin use

The following preferred terms will be grouped as "Phenytoin": phenytoin, phenytoin sodium, ethotoin, fosphenytoin, fosphenytoin sodium, and zentronal.

3.2.4.2 Valproate use

The following preferred terms will be grouped as "Valproate": valproic acid, valproate semisodium, valproate sodium, valproate magnesium, ergenyl chrono, and valproate.

3.2.4.3 Phenobarbital use

The following preferred terms will be grouped as "Phenobarbital": phenobarbital, phenobarbital sodium, methylphenobarbital, and primidone.

3.3 Definition of Baseline values

The baseline data for rollover subjects in EP0012 will not be recalculated. For subjects who are direct enrollers, some baseline variables may be calculated in SP0982 but these calculations need to be reassessed as detailed below.

For PGTCS data, the Combined Baseline Period is defined as the combined 12-week Historical and 4-week Prospective Baseline Periods from the SP0982 study. The Combined Baseline Period starts 84 days prior to Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. This means that for subjects who directly enrolled into EP0012 (were not randomized in SP0982), the baseline PGTCS (before first dose in EP0012) data from SP0982 is combined with any reported baseline seizure information from EP0012 to recalculate the subject's baseline variables such as PGTCS frequency.

Data from Combined Baseline is used for analyses involving PGTCS since the CRF was specific in asking for PGTCS counts. Other seizure type data recorded in Historical Baseline are deemed less reliable. For seizure calculations involving Absence, Myoclonic, Generalized (seizure type=II) and All seizure types (seizure types = I, II and III), Prospective Baseline data is used; that means for generalized and all seizure type calculations specifically, PGTCS data in Prospective Baseline will only be used (not the Combined Baseline data) along with the other seizure types.

For absence, myoclonic, generalized and all seizure data, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. This means that for the subjects who directly enrolled into EP0012 (were not randomized in SP0982), the baseline absence, myoclonic, generalized or all (respectively) seizure data from SP0982's Prospective Baseline period is combined with any reported baseline absence, myoclonic, generalized or all (respectively) seizure information in the daily seizure diary from EP0012 (reported before first dose in EP0012) to recalculate the subject's baseline variables such as days with absence, myoclonic, generalized or all seizures per 28 days.

In order to determine emergence of new seizure type, the Combined Baseline Period as well as any seizures reported prior to first dose for direct enrollers in EP0012 will be used.

For all other data, Baseline values are defined as follows;

- For direct enrollers from SP0982, data collected at Visit 1 prior to the first dose of study medication will be used as Baseline values. Data collected on the date of first dose of study medication will be assumed to be prior to the first dose. For data not collected at Visit 1 but still prior to the first dose of study medication, the last data collected in SP0982 will be used as Baseline values, if available.
- For rollover subjects from SP0982, the last non-missing value prior to the first dose of study medication in the SP0982 study will be used as the Baseline value.

For quantitative ECG assessments, if repeat measurements pre-first dose, then the average value is used as the Baseline value.

For direct enrollers, data that is used as the Baseline will be labelled as such. In general, change from baseline for these subjects will be calculated from Visit 2 onward, if the subject has a calculated baseline.

For rollover subjects, change from baseline for these subjects will be calculated from Visit 1 onward, if the subject has a baseline calculation from SP0982.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined in the Specification of Protocol Deviation (SPD) document. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

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

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

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock. A list of subjects with important protocol deviations will be agreed upon during the quarterly IPD meetings and will be documented in the IPD meeting minutes.

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (covid-19) will be documented. Important protocol deviations related to COVID-19 will be included in the important protocol deviations.

3.5 Analysis sets

Efficacy variables will be summarized using the FAS and safety variables will be summarized using the Safety Set (SS).

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have a signed Informed Consent/Assent form. Subjects completing SP0982 Safety Follow-up in EP0012 are contained in this analysis population because no study medication is administered to them.

3.5.2 Safety Set

The Safety Set (SS) is a subset of the ES and consists of all subjects who received at least 1 dose of LCM during EP0012. All safety analyses will be performed on the SS.

3.5.3 Full Analysis Set

The FAS is a subset of the SS and consists of all subjects with seizure diary data for at least 1 day during EP0012. PGTCS-related analyses will be performed on the FAS.

3.6 Treatment assignment and treatment groups

All subjects, except those enrolled to complete Safety-Follow-up in EP0012, will receive LCM.

At Visit 1, rollover subjects will start on a dose of LCM as follows;

- 10mg/kg/day for pediatric subjects weighing <30kg,
- 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg,
- 400mg/day (200mg twice a day (bid)) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Subjects who are direct enrollers into EP0012 will start at Visit 1 on a dose of LCM as follows;

- 2mg/kg/day for pediatric subjects weighing <50kg,
- 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction as detailed in the protocol.

All summaries will be presented with an overall all subjects treatment group.

3.7 Center pooling strategy

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

3.8 Coding dictionaries

Medical history and 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 Dictionary (WHO-DD SEP/2013). Medical procedures will not be coded. All coding will be completed prior to database lock.

3.9 Changes to protocol-defined analyses

There are no changes to analyses specified in the protocol however there are additional variables defined in the SAP which are detailed in Section 2.2.2.4 that will be analyzed.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The analyses will not include any covariates.

4.2 Handling of dropouts or missing data

For subjects missing data at the first visit in EP0012, data from SP0982 will be checked as follow:

- for subjects who are rollovers from SP0982 to EP0012, final clinic visit data in SP0982 will be checked for data expected and not reported for V1 in EP0012.
- for subjects who are direct enrollers in EP0012, baseline data will be used from EP0012 V1 or any unscheduled visit (if prior to first EP0012 dose) or the latest data from the screening and baseline visits in SP0982 can be used (also if prior to first EP0012 dose).

4.2.1 Missing seizure diary days

For evaluations based on seizure diary data, imputation for missing data will not be performed. This means, for example, for an analysis for an interim data cut or for the final analysis, only seizure data for completed visits can be used in the analyses (i.e. study participants should not be assumed to have zero seizures between the time of the last-known visit and the interim cutoff; the subject will appear as having missing seizure information). The calculation of average 28-day seizure frequency or days with seizure per 28 days accounts for missing data by only evaluating days for which the data are available. Additionally for PGTC seizure calculations, PGTCS are not counted during gaps when LCM is not taken > 3 consecutive days.

4.2.1.1 Week 94 visit – seizure data

At Week 94, subjects switch from using daily seizure diaries (where every date is entered) to using a seizure log (where only non-zero seizures are logged by date). For subjects who continue past Week 94 in the study, if the date of the Week 94 visit is not logged on the daily seizure diary with a non-zero seizure count and it does not appear on the seizure log with a non-zero count, then it can be assumed that 0 seizures occurred on that date.

4.2.2 Incomplete dates for first epilepsy diagnosis

Month and year of the first epilepsy diagnosis are collected on the SP0982 CRF. To calculate the time since first epilepsy diagnosis at Screening, a complete date will be imputed as following:

- 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 (imputing 1st for the day if only month and year are collected).
- 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 (imputing 1st for the day if only month and year are collected).
- If both the month and year are missing then no imputation will be done.

4.2.3 Incomplete dates for adverse events and concomitant medications

The following rules are applied to impute partial start and stop dates for medications.

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollovers is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollovers is the same as the month and year of the start, then use the date of first dose for direct enrollers or first visit for rollover subjects.
- If only the year is specified, and the year of first dose for direct enrollers or first visit for rollover subjects 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 for direct enrollers or first visit for rollover subjects is the same as the year of the start date, then use the date of first dose for direct enrollers or first visit for rollover subjects.

- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose for direct enrollers or first visit for rollover subjects, then use the date of first dose for direct enrollers or first visit for rollover subjects.

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.

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

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

Imputation of Partial Onset Dates

- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollover subjects is not the same as the month and year of onset, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollover subjects is the same as the month and year of onset, then use the date of first dose for direct enrollers or first visit for rollover subjects
- If only the year is specified, and the year of first dose for direct enrollers or first visit for rollover subjects 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 for direct enrollers or first visit for rollover subjects is the same as the year of onset, then use the date of first dose direct enrollers or first visit for rollover subjects
- If the AE onset date is completely unknown, then use the date of first dose for direct enrollers or first visit for rollover subjects

Imputation of Partial Resolution Dates

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

4.2.4 Incomplete date for the last administration of study medication

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

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

If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the Study Termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the Study Termination CRF.

If a subject died and has a partial or missing last administration date, the date is 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 an unrealistic value for duration of exposure.

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

4.2.5 Missing adverse event intensity

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

4.2.6 Missing adverse event relationship to study medication

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

4.3 Interim analyses and data monitoring

No formal interim analysis is planned for this study. Interim data from EP0012 may be summarized to support a regulatory submission, regular safety signal detection monitoring, publications, and annual reports to regulatory agencies. For any interim data summaries, all available data as of the time of the clinical cut-off date will be included. Subjects ongoing at the time of an interim data summary will be assumed to be treated up to and including the date of the clinical data cut-off. No Data Monitoring Committee is planned.

4.4 Multicenter studies

Refer to Section 3.7.

4.5 Multiple comparisons/multiplicity

No adjustments for multiplicity are required as all analyses are descriptive only.

4.6 Use of an efficacy subset of subjects

No efficacy subsets are defined for statistical analyses.

4.7 Active-control studies intended to show equivalence

Not applicable for this study.

4.8 Examination of subgroups

Disposition will be presented by age at baseline in SP0982 subgroup for the SS and FAS. Exposure will be presented by age at baseline in SP0982 and region subgroups for the SS. Overall treatment emergent adverse events (TEAE) incidence will be presented by age at baseline in SP0982 subgroup for the SS.

The subgroups to be examined include:

- Age at Baseline in SP0982 (≥ 4 to <12 years of age, ≥12 to <18 years of age, 18 to <65, ≥65)
- Development (in EP0012) (≥ 4 to <18 years of age, ≥18)
- Region
  - North America: United States, Puerto Rico
  - Latin America: Brazil, Mexico
  - Western/Central Europe: Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain
  - Eastern Europe: Bulgaria, Romania, Russia, Turkey
  - Asia/Pacific/Other: Australia, China, Israel, Japan, South Korea, Taiwan.

The following scales are assessed by specific age subgroupings. The following age subgroupings are used for the purpose of summarizing the following scales:

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

Selected disposition and safety analyses will be presented by the age at enrollment into EP0012 for the purpose of addressing requirements set in Article 46 of the European Pediatric Regulation (see Section 11.5 for further details).

4.9 Data handling method of textual results in laboratory data

For laboratory data analysis, any textual data above the upper LOQ (eg. ">n.nnn") will be set to the upper LOQ and used when determining the maximum.

The original value will be displayed in subject data listings.

4.10 Use of a safety subset of subjects

For absence seizure analyses, the population analyzed will be further restricted to the subset of subjects

- who reported a seizure classification history of absence seizures in either SP0982 or EP0012, or

- who reported absence seizures during Combined Baseline Period, the Treatment Period or Transition Period of SP0982 or
- who reported absence seizures at any time prior to Safety Follow-up in EP0012.

These subjects are hereby referred to as the "Absence subpopulation" because this subgroup only contain subjects who have had or who are having absence seizures.

For myoclonic seizure analyses, the population analyzed will be further restricted to the subset of subjects

- who reported a seizure classification history of myoclonic seizures in either SP0982 or EP0012, or
- who reported myoclonic seizures during Combined Baseline period, the Treatment Period or Transition Period of SP0982 or
- who reported myoclonic seizures at any time prior to Safety Follow-up in EP0012.

These subjects are hereby referred to as the "Myoclonic subpopulation" because this subgroup only contain subjects who have had or who are having myoclonic seizures.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The study eligibility criteria and those subjects who did not meet it will be listed for the ES. All disposition data for the ES will be presented in subject data listings.

The number of subjects in the SS and FAS will be presented by investigator; the date of first subject in and date of last subject out will also be included in this summary. The subject populations will be listed.

The number and percentage of subjects in the ES, SS and FAS will be presented by age at Baseline in SP0982 as well as for all subjects.

The overall number and percentage of subjects who completed and discontinued from the study will be presented for the SS and FAS by age at baseline in SP0982 as well as all subjects including number and percentages for each reason for discontinuation. The completion of the study is defined as the completion of the Termination Visit. Discontinuation is defined as the completion of the ET Visit. The number and percentage of subjects who switch to commercial Vimpat use will be presented. The study termination information will be presented in the subject data listings.To assess what happens with subjects during the first 94 weeks of the study, the number and percentage of subjects who completed this time period, completed the study before 94 weeks and discontinued during this time period will be presented for the SS and FAS by age at baseline in SP0982 as well as all subjects including number and percentages for each reason for discontinuation during this time period.

The number and percentages of subjects impacted by COVID-19 will be presented for each visit, overall and by impact category, for all subjects in the SS. These data will be presented in subject data listings.

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

5.2 Protocol deviations

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

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

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

6.1.1 Derivation of demographics variables

6.1.1.1 Body mass index

BMI will be calculated using the following formula:

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

6.1.2 Analysis of demographics variables

Baseline demographics will be summarized for the SS and include gender, race, ethnicity, age, age category, height (cm), weight (kg) and BMI (kg/m^2); age is calculated in the SDTM as age at enrollment into EP0012 and that variable should be used for defining age category. Race and ethnicity will be from the SP0982 study but all other demographic variables will be from EP0012.

Demographics will be listed for all subjects enrolled.

6.2 Other Baseline characteristics

6.2.1 Derivation of other Baseline characteristics

6.2.1.1 Time since first diagnosis

The time since first diagnosis is calculated as follows:

the date of informed consent from SP0982 – the date of first epilepsy diagnosis from SP0982 / 365.25.

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

6.2.1.2 Age at diagnosis

Age at diagnosis of epilepsy will be calculated using the first epilepsy diagnosis date from SP0982 and the date of birth from EP0012. Imputation for partial dates of first epilepsy diagnosis and date of birth are described in Section 4.2.2 .

6.2.2 Analysis of other Baseline characteristics

For direct enrollers in EP0012, the baseline characteristic variables can represent a combination of baseline data stored in SP0982 as well as EP0012; the subjects continuing from SP0982 are included but their baseline data is from SP0982 only.

Subjects randomized in SP0982 will appear in summaries below denoted as being from "SP0982 entry". All subjects enrolled in EP0012 will appear in rows that have no reference to SP0982 and the rows denoted as being from "EP0012 entry" or "EP0012".

The following Baseline characteristics will be presented:

- Time since first diagnosis at date of consent – Time since first diagnosis calculated for all EP0012 subjects; this data is stored in SP0982
- Age at diagnosis of the disease – age at diagnosis calculated for all EP0012 subjects; this data is stored in SP0982ILAE Seizure classification history – see below
- Classification of epileptic syndrome – see below
- Lifetime AEDs and Benzodiazepines (EP0012) (0, 1-3, 4-6, 7+) – categorical representation of lifetime AEDs and Benzos of all EP0012 subjects
- Combined Baseline PGTCS frequency per 28 days (as continuous data) – baseline PGTCS seizure frequency from CRF of all EP0012 subjects; SP0982 IRT data is not used in EP0012.
- Combined Baseline PGTCS frequency categories (≤2, >2 per 28 days) – baseline PGTCS seizure frequency categorized from CRF of all EP0012 subjects
- Concomitant AEDs at EP0012 entry (0, 1, 2, 3, 4) – categorical representation of concomitant AEDs of all EP0012 subjects
- Concomitant benzodiazepine use at EP0012 entry (yes, no) – Yes/No to concomitant Benzo use of all EP0012 subjects
- LCM study drug status - continuing LCM treatment (randomized to LCM in SP0982), new LCM treatment (randomized to PBO or baseline failure from SP0982 or other)
- SP0982 exit status - Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up, SP0982 early discontinuation
- EP0012 entry status – Direct enroller, rollover.

ILAE Seizure Classification History (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized if it contains the same information as reported in SP0982; EP0012 and SP0982 information will be summarized if additional information is presented in either study. SP0982 information will be summarized if EP0012 contains no updated information.

Classification of Epileptic Syndromes (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized. SP0982 information will be summarized if EP0012 contains no updated information.

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

6.3 Subgroups

All subgroups detailed in Section 4.8 will be summarized in a table for the SS and FAS. Other subgroups that will be summarized using SP0982 baseline information are:

- Baseline age in SP0982 (4 to <12 years, 12 to < 18 years, 18 to < 65 years, ≥65 years)
- Age for PedsQL (4 years, 5 to 7 years, 8 to 12 years, 13 to <18 years)
- Age for Achenbach CBCL (4 to 5 years, 6 to 18 years)
- Age for BRIEF-P/BRIEF (4 years, 5 to 18 years).

Subgroup information will also be listed.

6.4 Medical history and concomitant diseases

Previous and ongoing medical history conditions, initially reported in SP0982 and potentially updated for EP0012, will be summarized by system organ class (SOC) and preferred term (PT) for the subjects in the SS. For medical history events, meaning they are not ongoing, if the same coded condition is reported in both SP0982 and EP0012, only the EP0012 condition will be summarized; if the coded conditions are differently reported in SP0982 and EP0012, then both sets of conditions will be summarized. If no new conditions are reported in EP0012, then only SP0982 conditions will be summarized. A similar summary will be provided for concomitant diseases for the SS. Concomitant diseases are medical history events which are ongoing at the SP0982 Screening Visit or reported as ongoing in EP0012 on the medical history CRF page.

The SP0982 and EP0012 data for the subjects in EP0012, including the SOC, PT and verbatim reported term, will also be presented in data listings. A glossary of medical history SOC and PTs will also be completed.

6.5 Prior and concomitant medications

Medications with a start date before the first dose of study medication for direct enrollers will be considered prior medications. Medications taken on or after the date of the first dose of study medication will be considered concomitant medications; medications taken by rollover subjects which are ongoing and concomitant in SP0982 will be considered concomitant in EP0012. Medications with a missing start date whose stop date is either unknown or after the date of the first dose of study medication will be considered concomitant. Medications with a missing start date whose stop date is prior to the date of the first dose of study medication will be considered as prior medications. Prior AEDs, benzodiazepines and other medications are not summarized for the EP0012 subjects.

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

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

Concomitant AEDs and benzodiazepines taken during the Treatment Period will be summarized by ATC level 4 and PT for the SS.

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

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

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

The number of subjects entering EP0012 on or withdrawing to Monotherapy during the Treatment Period will be identified. Entering EP0012 on Monotherapy means the subject has no documented AEDs that are ongoing at first visit. Withdrawing to monotherapy means the subject has documentation that all background AEDs [except LCM] were discontinued during Treatment Period. A record for the discontinued background AEDs must be present in the concomitant AED data and study medication must be taken continuously (>3 day gaps are not allowed). For the subjects who withdrew to monotherapy, the following results will be listed:

- Exposure
- Monotherapy Start Date
- Monotherapy End Date
- Duration (days) of monotherapy
- Concomitant AEDs that were discontinued
- Period when monotherapy starts (0 to Week 46 (V8), >Week 46 to Week 94 (V11), >Week 94 to Week 142 (V13), >Week 142 to Week 190 (V15), >Week 190 (V15)).

The Monotherapy period and the cutoffs are determined for any visit falling within the Treatment Period, after using the definition of Treatment Period from Section 3.2.1.1 and the visit algorithm from Section 3.2.1.7. The start of the Monotherapy period is mapped to the period based on the subject's visit schedule as denoted in the period cutoffs (V8, V11, V13, and V15).

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance cannot be derived. Compliance data for oral solution as collected on the eCRF will be included in subject data listings. Compliance for tablet form of study medication is not collected.

8 EFFICACY ANALYSES

Analyses of the efficacy variables (i.e. PGTCS-related variables) will be performed using the FAS (unless otherwise stated) and will be descriptive in manner only. Efficacy analyses will be performed on data reported during the efficacy analysis Treatment Period. PGTCS analyses will be performed on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 days, any PGTCS reported during the gap will not be included in PGTCS summaries.

Subject seizure information will be imputed with all dates between the start and end of the efficacy Treatment Period; for years 3-5, all days are assumed zero seizure days except those with Not Dones or non-zero counts. Seizure frequency and seizure days will be calculated over non-missing (or evaluable) seizure diary days. Diary days captured as Not Done will not be

considered in the calculation of seizure frequency or days with seizure (i.e. unevaluable). Because the evaluation of efficacy is not the primary objective of this study, and because in an uncontrolled study in a variable setting, which allows individualized optimization of study medication and concomitant AEDs, no summaries assessing the impact of missing seizure diary days are planned.

Other seizure variables are considered safety variables and the analysis will be performed using the SS spanning the Treatment Period.

All seizure diary data will be listed. A listing of subjects excluded from the FAS will also be produced.

8.1 Statistical analysis of the primary efficacy variable

No primary efficacy variables are defined for this study.

8.2 Statistical analysis of the secondary efficacy variable

8.2.1 Derivation of secondary efficacy variable

The secondary efficacy variable, calculated on the FAS, is percent change in PGTCS frequency per 28 days from Combined Baseline Period for PGTCS data where there is no >3 day LCM gap. In order to account for potential differences in the durations of the study periods for individuals, seizure data will be normalized to 28 days. For years 1-2, (up to and including Visit 11 date), seizure information is collected every day, but for years 3-5 only days with a seizure are recorded. Therefore, from the day after Visit 11 date (inclusive) to the date of the end of the efficacy Treatment Period (inclusive) will be assumed to be seizure free days unless non-zero seizure counts are recorded or the seizure diaries are recorded as being Not Done for those days. For years 1-2, only days with a seizure record other than Not Done are considered evaluable. Also see Section 4.2.1.

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

SF =

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

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

PCH = [(SFT – SFCB) / SFCB] x 100

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

8.2.2 Analysis of secondary efficacy variable

The percent change in PGTCS frequency during the efficacy Treatment Period by Completer Cohort and Time Period will be summarized with descriptive statistics. All calculated completer cohorts and time periods will be summarized.

The percent change in PGTCS frequency over the efficacy Treatment Period by Time Period will be summarized with descriptive statistics. All calculated time period results will be summarized.

All PGTCS frequency per 28 days data will be listed.

8.3 Analysis of seizure related other efficacy variables

All seizure data recorded during the Treatment Period will be summarized and listed for the seizure-related other efficacy variables. Analyses of the other efficacy variables (i.e. absence, myoclonic, generalized and/or all seizure related variables) will be performed using the SS and will be descriptive in manner only. These analyses will be performed on data reported during the Treatment Period.

8.3.1 Derivations of seizure related other efficacy variables

8.3.1.1 Variable: Days with seizures per 28 days

All calculations involving days with seizures per 28 days will be on the SS.

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

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

For years 1-2 (up to and including Visit 11 date), only days with a seizure record other than Not Done are considered evaluable. However, for years 3-5, from the day after Visit 11 date (inclusive) to the date of the end of the efficacy Treatment period (inclusive) will be assumed to be seizure free days if no seizures are recorded or the seizure diaries are not recorded as being Not Done for those days..

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

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

PCH = [(DT – DPB) / DPB] x 100

where DT corresponds to the number of days with absence seizures per 28 days during the relative period and DPB corresponds to the number of days with absence seizures per 28 days during the Prospective Baseline Period. If DPB is zero, then PCH will be missing and any such subjects will be excluded from the percent change summary.

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

8.3.1.2 Variables: Responder status – reduction in PGTCS frequency

These variables are calculated on the FAS. A 50% responder is defined as a subject experiencing ≥50% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest. Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1. A 75% responder is defined as a subject experiencing ≥75% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

8.3.1.3 Variables: Responder status – reduction in days with absence seizures

These variables are calculated on the Absence subpopulation of the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period.

8.3.1.4 Variables: Responder status – reduction in days with myoclonic seizures

These variables are calculated on the Myoclonic subpopulation of the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period.

8.3.1.5 Variables: Responder status – reduction in days with generalized seizures

These variables are calculated on the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with generalized (all type II) seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting generalized seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with generalized seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with generalized seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting generalized seizures during the Prospective Baseline Period.

8.3.1.6 Variables: Responder status – reduction in days with all seizures

These variables are calculated on the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with all types of seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting any seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with all seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with all seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting any seizures during the Prospective Baseline Period.

8.3.1.7 Variables: Seizure-free status

For all seizure types and all subjects, any missing or Not Done day in the seizure diary renders a subject to be not seizure-free on that day due to the lack of information.

8.3.1.7.1 Variable: PGTCS free status

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary and seizures were assessed (ie, "no seizures" is marked or number is entered as zero). Days in the seizure diary which are marked as "not done" on the CRF will not be counted as a seizure-free day from PGTCS. A subject with a >3 day LCM gap within the period of interest will not be PGTCS-free for that period.

PGTCS free status will be summarized by completer cohort on the FAS. A subject will have seizure-free status from PGTCS for a completer cohort if the subject are in the completer cohort and reported only "no PGTC seizures" for all days during the completer cohort period. If 1 or more PGTCS are reported in the completer cohort or if the seizure data is Not Done, then the subject has PGTCS free status=No for the completer cohort.

8.3.1.7.2 Variable: Generalized seizure-free status

If missing data is reported, then the subject is not seizure-free from generalized seizures for those missing days.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero seizure type=II seizures and no "Not Done" days during the time period for the SS. If 1 or more seizure type=II seizures are reported or if there are "Not Done" seizure diary days in the time period, then the subject has generalized seizure-free status=No for the time period.

8.3.1.8 Variables: All Seizure-free status

A seizure-free day from all seizures will be defined as a day where no seizures (seizure type=I, II or III) were reported in the seizure diary.

A subject will have seizure-free status from all seizure types for the applicable time period if the subject completed the time period and reported zero seizures, with no "Not Done" days, during the time period for the SS. If 1 or more seizures are reported or if there are "Not Done" seizure diary days in the time period, then the subject has all seizure-free status=No for the time period.

8.3.1.9 Variable: Worsening of PGTCS

Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1 on the FAS. PGTCS worsening is defined as a subject experiencing ≥50% increase in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

8.3.1.10 Variable: Worsening of days with absence seizures

Response to treatment will be based on the percent change in days with absence seizures per 28 days on the Absence subpopulation, as calculated in Section 8.3.1.1 on the SS. Worsening is

defined as a subject experiencing ≥50% increase in days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period.

The increase in days with absence seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period.

8.3.1.11 Variable: Worsening of days with myoclonic seizures

Response to treatment will be based on the percent change in days with myoclonic seizures per 28 days on the Myoclonic subpopulation, as calculated in Section 8.3.1.1 on the SS. Worsening is defined as a subject experiencing ≥50% increase in days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period.

The increase in days with myoclonic seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period.

8.3.1.12 Variable: Worsening of days with generalized seizures

Response to treatment will be based on the percent change in days with generalized seizures per 28 days, as calculated in Section 8.3.1.1 on the SS. Worsening is defined as a subject experiencing ≥50% increase in days with generalized seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting generalized seizures during the Prospective Baseline Period.

8.3.1.13 Variable: Worsening of days with all seizures

Response to treatment will be based on the percent change in days with all seizures per 28 days, as calculated in Section 8.3.1.1 on the SS. Worsening is defined as a subject experiencing ≥50% increase in days with all seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting all seizures during the Prospective Baseline Period.

8.3.1.14 Variable: PGTCS free intervals

PGTCS-free intervals will only be assessed for periods not containing >3 day LCM gap. If the >3 day LCM gap appears in the period of interest, the subject is not PGTCS-free for the interval.

For the FAS, subjects who are PGTCS-free from the date of Visit 1 will be identified as having a PGTCS-free interval from Visit 1. The duration of the PGTCS-free interval will be calculated as date of last day of consecutive PGTCS freedom – date of Visit 1 +1.

To determine the longest interval of PGTCS-freedom, all PGTCS-free intervals will be identified with a calculation of date of last day of PGTCS freedom for Nth interval – date of the first day of PGTCS freedom for the Nth interval + 1. The largest duration of all N intervals will be identified as the longest interval of PGTCS freedom.

To determine the total duration of PGTCS-freedom, all N PGTCS-free intervals will be summed.

8.3.1.15 Variable: Generalized seizure free intervals

For the SS, subjects who are generalized seizure-free from the date of Visit 1 will be identified as having a generalized seizure-free interval from Visit 1. The duration of the generalized seizure-free interval will be calculated as date of last day of consecutive generalized seizure freedom – date of Visit 1 +1.

To determine the longest interval of generalized seizure free, all generalized seizure-free intervals will be identified with a calculation of date of last day of consecutive generalized seizure freedom for Nth interval – date of the first day of generalized seizure freedom for the Nth interval + 1. The largest duration of all N intervals will be identified as the longest interval of generalized seizure freedom.

To determine the total duration of generalized seizure freedom, all N generalized seizure-free intervals will be summed.

8.3.1.16 Variable: All seizure-free intervals

For the SS, subjects who are all seizure-free from the date of Visit 1 will be identified as having an all seizure-free interval from Visit 1. The duration of the all seizure-free interval will be calculated as date of last day of consecutive all seizure freedom – date of Visit 1 +1.

To determine the longest interval of all seizure free, all seizure-free intervals will be identified with a calculation of date of last day of consecutive all seizure freedom for Nth interval – date of the first day of all seizure freedom for the Nth interval + 1. The largest duration of all N intervals will be identified as the longest interval of all seizure freedom.

To determine the total duration of all seizure freedom, all N all seizure-free intervals will be summed.

8.3.2 Analysis of seizure-related other efficacy variables

8.3.2.1 Analysis: Days with seizures per 28 days

The following data will be summarized on the SS by all periods calculated for the Time Period or Completer Cohort with descriptive statistics only:

- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period

- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort.
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort.
- Percent change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort.
- Percent change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period

All seizure days data for absence, myoclonic, generalized and all seizures will be listed. Analyses of the absence seizure related variables will summarize the Absence subpopulation. Analyses of the myoclonic seizure related variables will summarize the Myoclonic subpopulation.

8.3.2.2 Analysis: Responder status – reduction in PGTCS frequency

The number and percentage of ≥50% and ≥75% responders in PGTCS will be summarized on the FAS by Time Period and Treatment Period.

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

The number and percentage of ≥50% and ≥75% responders will be summarized on the Absence subpopulation in the SS by Time Period and Treatment Period.

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

The number and percentage of ≥50% and ≥75% responders will be summarized on the Myoclonic subpopulation in the SS by Time Period and Treatment Period.

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

The number and percentage of ≥50% and ≥75% responders will be summarized on the SS by Time Period and Treatment Period.

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

The number and percentage of ≥50% and ≥75% responders will be summarized on the SS by Time Period and Treatment Period.

8.3.2.7 Analysis: Seizure free status

The number and percentage of subjects with seizure-free status (yes/no) will be summarized by Completer Cohort for the following types of seizures:

- Seizure-free status (yes, no) for PGTCS on the FAS
- Seizure-free status (yes, no) for all generalized seizure types on the SS
- Seizure-free status (yes, no) for all seizure types on the SS.

8.3.2.7.1 Analysis: PGTCS free intervals

The duration of the following PGTCS-free intervals during the Treatment Period on the FAS will be summarized with descriptive statistics:

- 1st PGTCS free interval from Visit 1
- Longest PGTCS-free interval
- All PGTCS-free intervals

8.3.2.7.2 Analysis: Generalized seizure free intervals

The duration of the following generalized seizure-free intervals during the Treatment period on the SS will be summarized with descriptive statistics:

- 1st generalized seizure-free interval from Visit 1
- Longest generalized seizure-free interval
- All generalized seizure-free intervals

8.3.2.7.3 Analysis: All seizure free intervals

The duration of the following all seizure-free intervals during the Treatment period on the SS will be summarized with descriptive statistics:

- 1st all seizure-free interval from Visit 1
- Longest all seizure-free interval
- All seizure-free intervals

8.3.2.8 Analysis: PGTCS worsening

The number and percentage of subjects with seizure worsening, ≥50% increase in PGTCS frequency per 28 days, will be summarized on the FAS by Time Period and Treatment Period.

8.3.2.9 Analysis: Worsening in days with absence seizures

The number and percentage of subjects with ≥50% increase in days with absence seizures per 28 days will be summarized on the Absence subpopulation in the SS by Time Period and Treatment Period.

8.3.2.10 Analysis: Worsening in days with myoclonic seizures

The number and percentage of subjects with ≥50% increase in days with myoclonic seizures per 28 days will be summarized on the Myoclonic subpopulation in the SS by Time Period and Treatment Period.

8.4 Analysis of health outcome other efficacy variables

8.4.1 Derivations of health outcome other efficacy variables

8.4.1.1 QOLIE-31-P variables

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

The QOLIE‑31‑P total score, subscale scores, and health status item score are calculated according to the scoring algorithm defined in Section 11.1 which accounts for the possibility of missing values. Scores range from 0 to 100 and higher scores indicating better functioning. QOLIE- 31-P data that are completely missing will not be replaced.

Subscale scores

As a first step to calculating the subscale scores, the individual responses for the 30 subscale items are rescaled to a 0 to 100 scale with higher scores reflecting better functioning; the rescaled values for each item are defined in Section 11.1. Each subscale score is then calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Total score

Total score is calculated as a weighted sum of the subscale scores based on the weighting in Section 11.1. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

Health status item

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

Distress items

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

Prioritization item

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

8.4.1.2 PedsQL variables

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations (<18 years), including those with acute or chronic health conditions. Only whole year ages are used. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≤4 years of age. The PedsQL Measurement Model includes developmentally appropriate forms for pediatric subjects >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. For each subject, the same version that is used at Baseline should be used for 12 months and thereafter the appropriate age versions should be used.

PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. For versions intended for subjects >8 years of age, Physical Functioning refers to questions [redacted] Emotional Functioning refers to questions [redacted] Social Functioning refers to questions [redacted] School Functioning refers to questions [redacted]

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

Item transformed score = 100 – (item raw score x 25)

Each PedsQL scale or dimension score is then calculated as the mean of the transformed item scores from items of the considered dimension. In the case of item-level missing data, these will be replaced by the average of non-missing item scores from the considered dimension, if at least 50% of the items from that dimension are non-missing.

The above algorithm will also be used to calculate the PedsQL total score (all items), the psychosocial health summary score (a combination of the emotional, social and school functioning items), and the physical health summary score (the physical functioning items) for each subject. These summary scores will be missing if any of the scale scores contributing to their calculation is missing.

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

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

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

- No problem = 1

- Some or moderate problems = 2
- Extreme problems = 3

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

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

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

The mapped utility values will make up the utility variable.

8.4.1.4 Hospital stays

An event logged on the Hospitalization/Emergency Room (ER) Visit form of the eCRF where "Emergency room" is marked as initial entry point will be defined as an ER visit. An ER visit with a subject transfer to an inpatient general ward will also be counted as a hospitalization. However, all other instances of ER visits (where subject transfer is not to an inpatient general ward) will not be counted as hospitalizations.

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

8.4.2 Analysis of health outcome other efficacy variables

8.4.2.1 QOLIE-31-P variables

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

The observed values and the changes from Baseline will be summarized descriptively for the total score, the subscale scores, health score and the distress items for each visit and Last Visit. The mean observed values for the prioritization items will also be summarized for each visit and Last Visit. The scores for individual subscales will only be analyzed when a total score can be calculated (ie, all subscales have a non-missing score). Individual questions will not be summarized. Individual questions, subscale scores, and total scores will be presented in subject

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

8.4.2.2 PedsQL variables

The observed values and change from Baseline for the total scale score and each of the 4 scale scores will be summarized for each visit and Last Visit. If a subject has a baseline calculated for the 2-4 year old PedsQL, due to the difference in questionnaires, this baseline should not be used for calculating change from baseline for the older aged questionnaires. For the 5-7 year old, 8-12 year old and 13-18 year old questionnaires, if the baseline was calculated from an younger aged questionnaire (except the 2-4 year old questionnaire) as the subject ages from 8 through 18 years old, change from baseline can use the younger aged baseline.

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

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

The observed values for each dimension and the mapped utility values will be summarized for each visit and Last Visit.

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

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

8.4.2.4 Concomitant medical procedures

Subjects who had any concomitant medical procedures during the course of the study based on the Concomitant Medical Procedures eCRF will be listed.

8.4.2.5 Healthcare provider consultations

All healthcare provider consultations data will be listed.

8.4.2.6 Hospital stays

All hospitalization/ER data will be listed.

8.4.2.7 Number of working or school days lost due to epilepsy

All working or school days lost data will be listed.

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

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

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

10 SAFETY ANALYSES

Any data that appears in the database (in UCB Findings, Clinical Events, or Findings About) and is not covered by the sections below, will be listed.

10.1 Extent of exposure

10.1.1 Derivation of exposure variables

Study medication treatment duration (days) will be calculated as follows for direct enrollers:

(last study medication dose – first study medication dose) + 1 day.

Study medication treatment duration (days) will be calculated as follows for rollover subjects:

(last study medication dose – visit 1 date) + 1 day. Gaps in treatment or days with unknown dosing will not be subtracted from the duration of exposure.

Subject-years of exposure is the total study medication treatment duration in days divided by 365.25.

The maximum daily LCM dose (mg/day and mg/kg/day) is defined as the highest total daily dose a subject received during the exposure period in the study.

Lacosamide modal dose will be defined as the daily LCM dose the subject received for the longest duration during the Treatment Period. 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). If a subject was on two different LCM doses for the same duration of time (ie, a tie when calculating modal dose), the modal dose will be set to the lower of the doses.

Duration at modal dose (days) will be defined as the date of the last dose of the modal dose minus the date of the first dose of the modal dose plus 1 day.

Because some pediatric subjects take both LCM formulations, dosing will be presented for all subjects within the formulation taken; this will be presented as raw dosing and some pediatric subjects will be summarized in both formulations. For pediatric subjects who take both LCM formulations, their tablet dosing in mg/day will be converted to mg/kg/day by dividing the total daily dose in mg/day by the most recently available (relative to the dosing date) body weight in kg; this will be presented as converted dosing and the summaries of subject data by formulation will be mutually exclusive. Should a subject receive both oral solution and an oral tablet on the same day, then the individual tablet dose in mg is converted to mg/kg by dividing by the most recently available (relative to the dosing date) body weight, and then the individual dose of oral solution in mg/kg is added to the tablet dose in mg/kg to obtain a total daily dose in mg/kg/day.

10.1.2 Analysis of exposure variables

The following LCM exposure summaries will be presented:

- Number and percentage of subjects and subject-years of exposure by 6-month time intervals (ie, >0, ≥6, ≥12, ≥18, ≥24, ≥30, ≥36, ≥42, ≥48, ≥54, and ≥60 months) and modal dose
- Number and percentage of subjects within each LCM treatment duration category by modal dose and maximum daily dose. LCM treatment duration categories (days) are as follows: 1 to 84; 85 to 168; 169 to 336; 337 to 504; 505 to 672; 673 to 1008; 1009 to 1344; 1345 to 1680; >1680; any duration (total of durations). The LCM dose categories for oral solution are as follows: 0mg/kg/day/Unknown, >0 to <4mg/kg/day, ≥4mg/kg/day to <8mg/kg/day, and ≥8mg/kg day. The LCM dose categories for tablets are as follows: 0mg/day/Unknown, >0 to

<200mg/day, ≥200 to <400mg/day, ≥400 to <600mg/day, ≥600 to 800mg/day, and ≥800mg/day.

Summary statistics will be presented for treatment duration (days), maximum daily dose (mg/day and mg/kg/day) and modal dose (mg/day and mg/kg/day). This analysis will be repeated for each subgroup as detailed in Section 4.8.

Pediatric subjects with oral solution (mg/kg/day) and tablet (mg/day) dosing will be summarized two ways: raw (mg/kg/day and mg/day) and converted (mg/kg/day only).

Detailed LCM exposure, LCM dosing, and drug accountability will be presented in subject data listings. In addition, a listing of subject numbers with exposure ≥800mg/day for adults, >600mg/day for pediatrics taking tablets and >12mg/kg/day for pediatrics taking oral solution at least once during the Treatment Period will be provided.

10.2 Adverse events

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

Adverse events will be considered treatment-emergent if the event had onset on or after the date of the first study medication dose in EP0012 and within 30 days following the last study medication dose or events whose intensity worsened on or after the date of first study medication dose and within 30 days following the date of last study medication administration. Adverse events which were ongoing and treatment-emergent in SP0982 will remain treatment-emergent in EP0012 for rollover subjects.

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

Only TEAEs that start on or after the date of Visit 1 will be summarized in tables (ie, ongoing AEs from the SP0982 study will not be considered treatment emergent). AEs that start in SP0982 but worsen in EP0012 will be recorded in the EP0012 database with a new start date.

The following summaries will be presented:

- Overview of TEAEs
- Overview of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs
- Incidence of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs by intensity
- Incidence of TEAEs by relationship
- Incidence of serious TEAEs

- Incidence of serious TEAEs – Subject numbers
- Incidence of TEAEs leading to discontinuation of subjects
- Incidence in TEAEs leading to discontinuation of subjects – Subject numbers
- Incidence of other significant TEAEs (See Section 11.2 for details)
- Incidence of TEAEs for potential drug-induced liver injury (PDILI) (See Section 11.2 for details)
- Incidence of TEAEs by 100 person-months of exposure during the study
- Incidence of TEAEs by 3-month exposure period of TEAE onset
- Incidence of TEAEs of interest related to epilepsy by 3-month exposure period of TEAE onset

The 100 person-months of exposure calculation takes the incidence of subjects with TEAEs, divides it by the total exposure in months and multiplies by 100. Exposure in days is divided by 28 days to get exposure in months.

To assess TEAEs related to epilepsy, PTs will be identified by ongoing manual medical review. The following PTs (including those identified from continuing medical review) will be summarized by 3-month periods of TEAE onset: petit mal epilepsy, myoclonus, and myoclonic epilepsy.

The dose at onset TEAE summaries will be presented by the LCM dosing categories presented in Section 10.1.2. Adverse events of unknown dosing are those with no known dose or known dosing and partial AE start or stop dates. TEAEs which were ongoing from SP0982 will be presented for the dose the subject was taking on the date of first dose in EP0012.

- Incidence of TEAEs by dose at onset
- Incidence of Serious TEAEs by dose at onset
- Incidence of TEAEs leading to discontinuation of subjects by dose at onset

Subject data listings will be presented for the following:

- Subjects experiencing adverse events on the ES
- Subjects experiencing serious TEAEs on the SS
- Subjects experiencing TEAEs leading to discontinuation of subjects on the SS
- Subjects experiencing adverse events leading to death on the ES

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

A list of further AE tables required for EudraCT and clinicaltrials.gov is provided in Section 11.5.

10.3 Clinical laboratory evaluations

Clinical laboratory parameters are used in analyses if more than two subjects per visit have a result. All clinical laboratory data appear in listings.

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

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

Treatment-emergent markedly abnormal (TEMA) values indicate significant deviations from the expected range of age-appropriate values. TEMA laboratory results are those that are observed post-Baseline during the Treatment Period but not present at Baseline. TEMA values for serum chemistry and hematology laboratory parameters are provided in UCB conventional (traditional) and standard units. The definition of TEMA values for hematology and chemistry values can be found in Section 11.3. The number and percentage of subjects with at least 1 TEMA value will be presented by scheduled visit, Last Visit, Early Termination Visit, minimum and maximum post-Baseline values obtained during the Treatment Period for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified. A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg, Pediatric subjects) for the markedly abnormal criteria.

A table summarizing the number of subjects meeting the potential drug induced liver injury (PDILI) criteria during the Treatment Period will also be presented. The categories for PDILI that will be presented are:

- ≥3xULN in ALT or AST and ≥2xULN total bilirubin and ≥2xULN of alkaline phosphatase
- ≥3xULN in ALT or AST and ≥2xULN total bilirubin
- ≥5xULN in ALT or AST
- ≥8xULN in ALT or AST
- ≥3xULN in ALT or AST and the presence of symptoms
- ≥3-<5xULN and baseline ≥2xULN in ALT or AST and <2xULN total bilirubin and no presence of symptoms
- ≥5xULN and baseline ≥2xULN in ALT or AST and <2xULN total bilirubin.

The National Cancer Institute common toxicity criteria (NCI CTC) version 4 can be found in Section 11.4. The number and percentage of subjects with treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher (hematology and clinical chemistry) will be summarized by laboratory parameter, and visit for the Treatment Period. Treatment emergent abnormalities of grade 2 or higher are those that were observed during the Treatment Period at

scheduled visits and not reporting a grade 2 or higher abnormality during the Baseline Period. All treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher will be presented in a subject number listing.

Subject data listings of all laboratory data will also be presented.

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

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

10.4.1 Vital signs

Observed values and changes from Baseline in vital sign parameters (pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight (kg), height (cm) and BMI (kg/m^2)), will be summarized using descriptive statistics for the scheduled visits. In addition, summary statistics for the observed value and change from Baseline will be presented for Last Visit, minimum, and maximum post-Baseline values obtained during the Treatment Period. Repeated or unscheduled assessments during the study will not be presented in by-visit summaries, but will be considered when determining the minimum, and maximum post-Baseline values during the Treatment Period.

Treatment emergent abnormalities of vital signs, the criteria that do not involve a comparison to baseline, are those that were observed during the Treatment Period at scheduled visits and not reporting the abnormality during the Baseline Period. The number and percentage of subjects with at least 1 TEMA value will be presented at each post-Baseline visit, Last Visit, Early Termination Visit and minimum and maximum post-Baseline values obtained during the Treatment Period. Percentages will be relative to the number of subjects with a value at each time point.

A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg. Pediatric subjects) for the TEMA criteria.

All TEMA results summarized will be presented in a subject number listing. The abnormal vital sign criteria are defined in Section 11.3.3.

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

10.4.2 Electrocardiograms

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

10.4.2.1 Derivation of corrected QT values

The Bazett corrected QT (QTcB) will be calculated as

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

The Fridericia corrected QT (QTcF) will be calculated as

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

10.4.2.2 Analysis of ECG parameters

For quantitative ECG measurements (heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT intervals using Bazett and Fridiricia correction methods), summary statistics of the actual values and change from Baseline (where Baseline is from SP0982 as defined in Section 0) will be summarized for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the TEMA ECG criteria age categories. Last visit is the value from the last post-baseline visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values and average value are listed. A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg, Pediatric subjects) for the continuous data.

The number and percentage of subjects who met each of the TEMA criteria specified in Section 11.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval, QRS interval, QT interval and corrected QT intervals by scheduled visits and Last Visit, Early Termination Visit, minimum and maximum post-Baseline values obtained during the Treatment Period. A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg, Pediatric subjects) for the TEMA criteria.

Repeated or unscheduled ECG assessments during the study will not be presented in by visit summaries, but will be considered when determining the last visit values during the Treatment Period. Subject numbers for those with TEMA ECG values will be listed by abnormality criteria.

The number and percentage of subjects with QT interval values classified as <450ms, 450 to <480ms, 480 to <500ms and ≥500ms and an increase from Baseline of <30ms, 30 to <60ms and ≥60ms will be summarized for uncorrected QT, QTcB, and QTcF by visit.

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

10.4.3 Physical examination

A listing of abnormal physical examination findings will be provided.

10.4.4 Tanner stage assessment

The investigator will evaluate the subject's sexual development using the 3-item Tanner scale (ie, for females: breasts, pubic hair, and overall stage; and for males: genitals, pubic hair, and overall stage). The investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner stage (ie, those subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study).

A shift table will be produced showing the change in Tanner stage (1 to 5) from Baseline to Last Visit during the first 2 years of the Treatment Period, by sex, for each of the 3-items. A shift table will also be produced for subjects enrolled > 2 years, showing the change in Tanner stage (1 to 5) from Baseline to Last Visit during the Treatment Period, by sex, for each of the 3-items.

A listing of Tanner stage assessments will be provided.

10.4.5 Neurological examination

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

10.4.6 Assessment of suicidality

Suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). This scale will be used for screening as well as to assess suicide ideation and behavior that may occur during the study. All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at the first visit and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version should be used at subsequent visits. The C-SSRS is not validated for subjects <6 years of age and will not be used for this population.

Subject data listings of the data for the C-SSRS where questions 4 or 5 was answered 'Yes' will be provided since this is a study withdrawal criteria. No summaries of the C-SSRS data are planned.

10.4.7 Achenbach Child Behavior Checklist

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. The Achenbach CBCL consists of the CBCL/1½-5 for children 4 years to 5 years and 11 months of age, and the CBCL/6-18 for children ≥6 years to <17 years of age. The version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: for subjects who completed the CBCL/1½-5 at the Baseline assessment of the previous study and turn 6 years of age within 1 year after the Baseline assessment of the primary study, the CBCL/1½-5 should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the CBCL/6-18

should be completed. The Achenbach CBCL will only be administered in countries where a validated translated version is available. For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range.

10.4.7.1 Derivation of Achenbach variables

The CBCL/1½-5 will be grouped according to syndrome scales in Table 1 and the CBCL/6-18 will be grouped according to empirically based syndrome scales in Table 2. The Achenbach CBCL has a 6-month recall. If a subject leaves the study early and has been in the study for less than 6 months, this subject's data will not be included in the analysis and will be listed only.

Table 1 CBCL/1½-5

Syndrome Scale	Questions
Aggressive behavior	8, 15, 16, 18, 20, 27, 29, 35, 40, 42, 44, 53, 58, 66, 69, 81, 85, 88, 96
Anxious/depressed	10, 33, 37, 43, 47, 68, 87, 90
Attention problems	5, 6, 56, 59, 95
Emotionally reactive	21, 46, 51, 79, 82, 83, 92, 97, 99
Sleep problems	22, 38, 48, 64, 74, 84, 94
Somatic complaints	1, 7, 12, 19, 24, 39, 45, 52, 78, 86, 93
Withdrawn	2, 4, 23, 62, 67, 70, 71, 98
Other problems	3, 9, 11, 13, 14, 17, 25, 26, 28, 30, 31, 32, 34, 36, 41, 49, 50, 54, 55, 57, 60, 61, 63, 65, 72, 73, 75, 76, 77, 80, 89, 91, 100

CBCL = Child Behavior Checklist

Table 2 CBCL/6-18

Syndrome Scale	Questions
Aggressive behavior	3, 16, 19, 20, 21, 22, 23, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104
Anxious/depressed	14, 29, 30, 31, 32, 33, 35, 45, 50, 52, 71, 91, 112
Attention problems	1, 4, 8, 10, 13, 17, 41, 61, 78, 80
Rule-breaking behavior	2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106
Social problems	11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79
Somatic complaints	47, 49, 51, 54, 56a, 56b, 56c, 56d, 56e, 56f, 56g

Syndrome Scale	Questions
Thought problems	9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100
Withdrawn/depressed	5, 42, 65, 69, 75, 102, 103, 111

CBCL = Child Behavior Checklist

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

0=not true (as far as known)

1=somewhat or sometimes true

2=very true or often true.

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

10.4.7.2 Analysis of Achenbach variables

Only the syndrome scales presented in Tables 1 and 2 will be analyzed. Raw scores and change from Baseline for each CBCL/1 ½ -5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Raw scores and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit. If a subject has a baseline calculated for the CBCL/1 ½ -5 syndrome, that baseline should not be used for calculating change from baseline for the CBCL/6-18 syndrome.

Calculated T-score values and change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Calculated T-score values and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

Subject data listings of the data for the Achenbach CBCL will be provided containing the calculated T-scores, raw scores and change from Baseline. The means of the calculated T-score will be plotted by visit.

10.4.8 BRIEF-P and BRIEF assessment

The BRIEF-P and BRIEF are validated tools that will be used for the evaluation of subjects ≥4 years to <5 years of age, and ≥5 years of age, respectively. The BRIEF-P or BRIEF appropriate for each subject's age should be completed, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment of the previous study and turn 5 years of age

within 1 year after the Baseline assessment of the primary study, the BRIEF-P should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the BRIEF should be completed. The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each developmentally appropriate version of the BRIEF subjects must have at least 1 year of data before transitioning to the next age range. The BRIEF-P and BRIEF have a 6-month recall. If a subject leaves the study early, and has been in the study for less than 6 months, this subject's data will not be included in the analysis and will be listed only.

10.4.8.1 BRIEF-P scores

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

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

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

Table 3 BRIEF-P questionnaire scoring

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

GEC = Global Executive Composite

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

Calculated T-score values and change from Baseline for the three index scores (Inhibitory self-control, flexibility and emergent metacognition), the 5 individual component scores and GEC for the BRIEF-P questionnaire will be summarized at each visit, and Last Visit.

All BRIEF-P assessment data will be listed including calculated T-scores, raw scores and changes from Baseline. The means of the BRIEF-P assessment data will be plotted by visit.

10.4.8.2 BRIEF scores

The BRIEF form comprises of 86 questions which can be answered as Never (scored as 1 point), Sometimes (scored as 2 points), and Often (scored as 3 points).

The first 72 items are included in the GEC score which ranges from 72 to 216, with higher scores reflecting poorer functioning.

The 2-subscale scores and 8 individual component scores that make up these subscale scores are outlined in Table 4.

Table 4 BRIEF questionnaire scoring

Scale/Index	Questions
Inhibit	38, 41, 43, 44, 49, 54, 55, 56, 59, 65
Shift	5, 6, 8, 12, 13, 23, 30, 39
Emotional Control	1, 7, 20, 25, 26, 45, 50, 62, 64, 70
Behavioral Regulation Index (BRI)	**All from {Inhibit, Shift, and Emotional Control}**
Initiate	3, 10, 16, 47, 48, 61, 66, 71
Working Memory	2, 9, 17, 19, 24, 27, 32, 33, 37, 57
Plan/Organize	11, 15, 18, 22, 28, 35, 36, 40, 46, 51, 53, 58
Organization of Materials	4, 29, 67, 68, 69, 72
Monitor	14, 21, 31, 34, 42, 52, 60, 63
Metacognition Index (MI)	**All from {Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor}**
GEC Score	**1-72**

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

The BRI score is the total of 28 items and ranges from 28-84. The MI score is the total of 44 items and ranges from 44 to 132.

T-score values and change from Baseline for the two indexed scores (BRI and MI), the GEC and the 8 individual component scores for the BRIEF questionnaire will be summarized at each visit, and Last Visit. If a subject has a baseline calculated for the BRIEF-P, that baseline should not be used for calculating change from baseline for the BRIEF.

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

All BRIEF assessment data will be listed including all scales/index scores (raw and T-scores, calculated and change from baseline). The means of the BRIEF assessment data will be plotted.

10.4.9 Safety Seizure Information

All analyses will use the relevant data in the SS. The analyses regarding Absence seizure information will be generated on the Absence subpopulation. The analyses regarding the Myoclonic seizure information will be generated on the Myoclonic subpopulation.

10.4.9.1 New Seizure Type or Worsening Over Time

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period with absence or myoclonic, respectively, indicated by the Seizure History Classification, but not experienced in the Combined Baseline Period, as recorded in the diary, will be summarized overall and by LCM study drug status by 1-month period of seizure onset.

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period but not experienced in Combined Baseline Period or in seizure classification history, as recorded in the diary, will be summarized overall and by LCM study drug status by 1-month period of seizure onset.

The number and percentage of subjects with new absence or myoclonic seizures in the Treatment Period, with absence or myoclonic, respectively, indicated by the Seizure History Classification but not experienced in the Combined Baseline Period as recorded in the diary in subjects with a history of absence or myoclonic seizures, respectively, or subjects with ≥50% increase in days with absence or myoclonic seizures, respectively, per 28 days as compared to Prospective Baseline Period (for those subjects with absence or myoclonic seizure data, respectively, reported in the Prospective Baseline Period in SP0982), will be summarized overall and by LCM study drug status by 1 month period of seizure onset.

The number and percentage of subjects with ≥50% increase in days in absence or myoclonic seizures as compared to Prospective Baseline Period (for those subjects with absence or myoclonic seizure data, respectively, reported in the Prospective Baseline Period in SP0982) will be summarized by 1-month period of seizure onset.

10.4.9.2 Increase in days with absence seizures

Response to treatment regarding absence seizures will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with absence seizures per 28 days during the Treatment Period compared to the Prospective Baseline Period (for those subjects with absence seizure data reported in the Prospective Baseline Period in SP0982) will be presented.

10.4.9.3 Increase in days with myoclonic seizures

Response to treatment regarding myoclonic seizures will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with myoclonic seizures per 28 days during the Treatment Period compared to the Prospective Baseline Period (for those subjects with myoclonic seizure data reported in the Prospective Baseline Period in SP0982) will be presented.

11 APPENDICES

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

The following outlines the calculation of the subscale scores for the QOLIE-31-P. The rescaled responses are provided for each item. The subscale scores are calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing

response. Note that the divisors shown assume that all items for each subscale have a response; the divisor will differ if there are missing responses. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Response Final Score

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

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

TOTAL : _____ ÷ 4 = _____

Cognitive Functioning

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

TOTAL : _____ ÷ 6 = _____

Medication Effects

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

TOTAL : _____ ÷ 3 = _____

Daily Activities/Social Functioning

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

TOTAL : _____ ÷ 5 = _____

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

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

11.2 Appendix 2: Adverse Events

11.2.1 List of other significant AEs

Table 5 Other Significant AEs

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

MedDRA Preferred Term
Ventricular flutter
Ventricular tachyarrhythmia
Implantable defibrillator insertion
Cardiac arrest
Brugada syndrome
Defect conduction intraventricular
Electrocardiogram QT prolonged
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behavior
Suicidal ideation
Suicide attempt
Intentional self-injury
Self injurious behavior
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder

MedDRA Preferred Term
Decreased appetite
Diet refusal
Hypophagia
Food aversion
Abnormal behaviour

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

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

Table 6 AEs for PDILI

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

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

Blood bilirubin abnormal
Blood bilirubin increased
Alanine aminotransferase increased
Aspartate aminotransferase increased

11.3 Appendix 3: Markedly abnormal values

11.3.1 Hematology

Table 7 Hematology Markedly Abnormal Values

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

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

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

11.3.2 Chemistry

Table 8 Chemistry - Markedly Abnormal Values

Parameter	Age Range	Unit (conventional)	Abnormality Criteria (conventional)	Unit (standard)	Abnormality Criteria (standard)
AST (SGOT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
Alkaline Phosphatase	4y - <10y	U/L	≥834	U/L	≥834
	10y - <17y		≥1761		≥1761
	≥17y		≥3.0 x ULN		≥3.0 x ULN
GGT	1y - <13y	U/L	≥66	U/L	≥66
	13y - <17y		≥126		≥126
	≥17y		≥3.0 x ULN		≥3.0 x ULN
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	1y - <17y	g/dL	<4.3 >12.0	g/L	<43 >120
	≥17y		<4.3 >13.0		<43 >130
Albumin	≥1y - <17y	g/dL	<2.4 >8.4	g/L	<24 >84
	≥17y		<2.6		<26
BUN	1y - <17y	mg/dL	≥36	mmol/L	≥12.852
	≥17y		≥40		≥14.28
Urea	≥1y	mg/dL	>60	mmol/L	>10.02
Creatinine	1y - <10y	mg/dL	>1.2	umol/L	>106.8
	10y - <16y		>1.8		>159.12
	≥16y		≥2.0		≥176.8

Parameter	Age Range	Unit (conventional)	Abnormality Criteria (conventional)	Unit (standard)	Abnormality Criteria (standard)
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 - <17y	mg/dL	<7.4 >11.7	mmol/L	<1.85 >2.925
	⩾17y		⩽7.6 ⩾11.0		⩽1.9 ⩾2.75
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112
Phosphorous	1y - <17y	mg/dL	<1.8 >7.4	mmol/L	<0.5814 >2.3902
	⩾17y		⩽2.0 ⩾6.0		⩽0.646 ⩾1.938
Potassium	⩾1y	mEq/L	⩽3.0 ⩾6.0	mmol/L	⩽3.0 ⩾6.0
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151
Glucose	>1m - <17y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99
	⩾17y		<50 ⩾200		<2.775 ⩾11.1
Total Cholesterol	≥1y	mg/dL	>250	mmol/L	>6.475
LDL (calculated)	1y - <17y	mg/dL	>140	mmol/L	>3.626
	⩾17y		>200		>5.18
HDL	>2y	mg/dL	<20	mmol/L	<0.518
Triglycerides	⩾1y	mg/dL	>300	mmol/L	>3.39
Uric Acid	1y - <13y	mg/dL	>6.5	umol/L	>386.62
	13y - <17y		>8.6		>511.528
	⩾17y		>9.5		>565.06
Thyroxine (T4)	⩾1y	ug/dL	⩽3.8 ⩾13.5	nmol/L	⩽48.9098 ⩾173.7585

Parameter	Age Range	Unit (conventional)	Abnormality Criteria (conventional)	Unit (standard)	Abnormality Criteria (standard)
Globulin	⩾1y	g/dL	<1.2 >5.3	g/L	<12 >53

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; GGT: gamma-glutamyltransferase; L = liter; LLN = lower limit of normal; m = month; mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = year.

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

11.3.3 Vital signs

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

Table 9 Vital Signs Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥120 and an increase from Baseline of ≥15 <60[a] >100 [a]
Systolic Blood Pressure (mmHg)	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20

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

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

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

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

11.3.4 ECG

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

Table 10 ECGs Abnormality Criteria

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	≥500
	≥12y	≥500 or ≥60 increase from Baseline
QTc(F) (ms)	3y-<12y	>440, or >15% increase from Baseline
	≥12y- <17y	>440, or >15% increase from Baseline
	≥17y	>450, >480 [a], >500 or ≥60 increase from Baseline
QTc(B) (ms)	3y-<12y	>450, or >15% increase from Baseline
	≥12y- <17y	>450, or >15% increase from Baseline
	≥17y	>450, >480 [a], >500 or ≥60 increase from Baseline
PR interval (ms)	3y-<12y	>180, or >25% increase from Baseline
	≥12y - <17y	>200, or >25% increase from Baseline
	≥17y	Treatment-emergent value >200, >220, >250
QRS interval (ms)	3y-<12y	>100, or >25% increase from Baseline
	≥12y - <17y	>110, or >25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	3y-<12y	<60, >130
	≥12y	<50, >120

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

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

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

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

11.4 Appendix 4: NCI CTC

Table 11 NCI CTC

Medical Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Blood/bone marrow					
Anemia	Hemoglobin	<LLN - 10.0 g/dL (C) <LLN - 6.2 mmol/L <LLN -100 g/L (S)	<10.0 - 8.0 g/dL (C) <6.2 - 4.9mmol/L <100 - 80g/L (S)	<8.0 g/dL (C) <4.9 mmol/L <80 g/L (S)	*
Neutrophil count decreased	Neutrophil count	<LLN - 1500/mm3 <LLN - 1.5 x10e9 /L (C) <LLN – 1.5G/L (S)	<1500 - 1000/mm3 <1.5 - 1.0 x10e9/L (C) <1.5 - 1.0G/L (S)	<1000 - 500/mm3 <1.0 - 0.5 x10e9/L (C) <1.0 - 0.5G/L (S)	<500/mm3 <0.5 x 10e9/L (C) <0.5G/L (S)
White blood cell decreased	White blood cell	<LLN - 3000/mm3 <LLN - 3.0x10e9/L (C) <LLN - 3.0G/L (S)	<3000 - 2000/mm3 <3.0 - 2.0x10e9/L (C) <3.0 - 2.0G/L (S)	<2000 -1000/mm3 <2.0 - 1.0x10e9/L (C) <2.0 - 1.0G/L (S)	<1000/mm3 <1.0 x 10e9/L (C) <1.0G/L (S)
Platelet count decreased	Platelet count	<LLN - 75,000/mm3 <LLN -75.0 x 10e9/L(C) <LLN -75.0G/L (S)	<75,000 - 50,000/mm3 <75.0 -50.0 x 10e9/L(C) <75.0 -50.0G/L (S)	<50,000 -25,000/mm3 <50.0 -25.0 x 10e9/L(C) <50.0 -25.0G/L (S)	<25,000/mm3 <25.0 x 10e9/L(C) <25.0G/L (S)
Lymphocyte count decreased	Lymphocyte count	<LLN-800/mm3 <LLN-0.8x10e9/L (C)	<800 -500/mm3 <0.8 – 0.5x10e9/L (C)	<500 - 200/mm3 <0.5 – 0.2x10e9/L (C)	<200mm3 <0.2x10e9/L (C)

Medical Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4
		<LLN-0.8G/L (S)	<0.8 – 0.5G /L (S)	<0.5 – 0.2G/L (S)	<0.2G/L (S)
Metabolic/chemistry					
GGT increased	Gamma glutaryl transferase	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hypercalcemia	Calcium, corrected serum	>ULN - 11.5 mg/dL (C) >ULN - 2.9mmol/L (S)	>11.5 - 12.5 mg/dL (C) >2.9 - 3.1mmol/L (S)	>12.5 - 13.5 mg/dL (C) >3.1 - 3.4mmol/L (S)	>13.5 mg/dL (C) >3.4 mmol/L (S)
Hypocalcemia	Calcium, corrected serum	<LLN - 8.0 mg/dL (C) <LLN - 2.0mmol/L (S)	<8.0 - 7.0 mg/dL (C) <2.0 - 1.75 mmol/L (S)	<7.0 - 6.0 mg/dL (C) <1.75 - 1.5mmol/L (S)	<6.0 mg/dL (C) <1.5 mmol/L (S)
Hyperglycemia	Glucose, fasting**	>ULN -160 mg/dL (C) >ULN - 8.9 mmol/L (S)	>160 -250 mg/dL (C) >8.9 - 13.9 mmol/L (S)	>250 - 500 mg/dL (C) >13.9 - 27.8mmol/L (S)	>500 mg/dL (C) >27.8 mmol/L (S)
Hypoglycemia	Glucose	<LLN - 55 mg/dL (C) <LLN - 3.0mmol/L (S)	<55 - 40 mg/dL (C) <3.0 - 2.2mmol/L (S)	<40 - 30 mg/dL (C) <2.2 - 1.7mmol/L (S)	<30 mg/dL (C) <1.7 mmol/L (S)
Hyperkalemia	Potassium	>ULN - 5.5 mmol/L (S)	>5.5 - 6.0 mmol/L (S)	>6.0 - 7.0 mmol/L (S)	>7.0 mmol/L (S)
Hypokalemia	Potassium	<LLN - 3.0 mmol/L (S)	*	<3.0 - 2.5 mmol/L (S)	<2.5 mmol/L (S)
Hypernatremia	Sodium	>ULN - 150 mmol/L (S)	>150 - 155 mmol/L (S)	>155 - 160 mmol/L (S)	>160 mmol/L (S)
Hyponatremia	Sodium	<LLN - 130 mmol/L (S)	*Not defined*	<130 - 120 mmol/L (S)	<120 mmol/L (S)
Hyper-triglyceridemia	Triglycerides	150 - 300 mg/dL (C) 1.71 - 3.42 mmol/L (S)	>300 - 500 mg/dL (C) >3.42 - 5.7 mmol/L (S)	>500 - 1000 mg/dL (C) >5.7 - 11.4 mmol/L (S)	>1000 mg/dL (C) >11.4 mmol/L (S)

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

Medical Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increased	Creatinine	>ULN - 1.5x ULN	>1.5 - 3.0x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN

C=Conventional units, LLN=lower limit of normal; S=Standard units, ULN=upper limit of normal.

The cutoffs are according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: 28 May 2009 (v4.03: 14 June 2010).

* In terms of the laboratory cut-offs, the criterion is the same as the preceding grade.

** Fasting status will be ignored when programming this criteria.

Note: Additional significant digits added to the mmol/L units (as published in Version 4.0) to be consistent with the umol/L units (UCB standard).

11.5 Appendix 5: Tables required for Article 41 (EudraCT)

Discontinuation due to AEs by Development

11.6 Additional Subgroups to be programmed in ADSL

The following subgroup variable will also be programmed:

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

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

12 AMENDMENT TO THE STATISTICAL ANALYSIS PLAN

12.1 Amendment 1

12.1.1 Rationale for the amendment

The SAP was amended to reflect changes adopted in SP0982 Protocol Amendment 5 and EP0012 Protocol Amendment 2. Here is a list of major changes:

- Minor editorial corrections were made such as changing the reference of "PGTCS seizure" to "PGTCS"
- The timing of completer cohort was changed from 6, 12 and 24 months to be in line with EP0012 visits at weeks 22, 46, and 94.
- Adding a 75% responder in addition to the 50% responder for PGTCS and days with absence and myoclonic seizures.
- Adding worsening in PGTCS and days with absence and myoclonic variables and analyses.
- Updating the new absence and myoclonic seizure emergence analysis
- Adding figures for QOLIE-31-P, PedsQL, EQ-5d-3L, BRIEF-P, BRIEF, Achenbach variables
- Clarifying the analyses for hematology, clinical chemistry and ECGs
- Adding and clarifying a few AE analyses
- Updating the list of Other Significant AEs
- Adding the list of AEs for potentially drug induced liver injury
- Updating the ECG markedly abnormal criteria
- Removing analyses intended to summarize study results for Years 1-2 and Years 3-5.

12.1.2 Modification and changes

12.1.2.1 Specific changes

The information below was revised from:

SAP/Amendment Number	Date
Final SAP	20 Dec 2016

Has been changed to:

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018

2.3, Study Design and Conduct, the following text was added as the 3rd paragraph:

For SP0982 subjects consented under Protocol Amendment 5, after the 125th event is confirmed, two classes of subjects will be allowed to enroll in EP0012. Subjects who are being screened

will be allowed to directly enroll into EP0012, thus their screening and baseline data will be captured in SP0982 but their treatment information will be captured in EP0012; baseline information from SP0982 will be used for these subjects in EP0012. For subjects who are concluding their LCM treatment and tapering in SP0982, these participants will be consented and complete their Safety Follow-Up (thus not receiving any LCM) in EP0012; the data captured in EP0012 will not be transferred to SP0982.

2.4 Determination of Sample Size, the paragraph was revised from:

The sample size of this open-label extension study will be determined by the parent SP0982 study, where approximately 200 subjects are planned to be randomized. SP0982 is an event-driven study. Up to 250 subjects may be enrolled to meet the required number of events. Baseline failures from SP0982 will also be eligible for EP0012, which may increase the sample size.

Has been changed to:

The sample size of this open-label extension study will be determined by the parent SP0982 study. SP0982 is an event-driven study. Up to 250 subjects may be enrolled to meet the required number of events. Baseline failures from SP0982, subjects in screening at the end of SP0982 and SP0982 subjects completing Safety follow-up in EP0012 will also be eligible for EP0012, which may increase the sample size.

Section 3.1, General presentation of summaries and analyses, the following text was added to the end of the 2nd paragraph:

for some parameters, Q1 and Q3 may also be displayed

Section 3.1, the following sentence was changed from:

- Minimum and maximum will have the same number of decimal places as the original value.

Was changed to:

- Minimum, Q1, Q3 and maximum will have the same number of decimal places as the original value.

Section 3.2.1.1, Analysis periods, the 2nd bullet was modified from:

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

Was changed to:

- Post-Treatment Period: The Post-Treatment Period is defined as the treatment free observational phase after the Treatment Period, for the subjects who take LCM in EP0012. It starts on the day after the end date of the Treatment Period and ends on the date of the final visit or date of last contact with the subject, whichever is later. For the subjects from SP0982 who are completing their Safety Follow-up in EP0012, their entire time in EP0012 will be deemed to be in the Post-Treatment Period due to the subjects not taking LCM in EP0012.

Section 3.2.1.4, Month, the following text was added:

A month is defined as 28 days.

Section 3.2.1.5, Completer Cohort, the section was revised from:

A completer cohort will be defined as the subset of subjects in the Full Analysis Set (FAS) that were enrolled and treated with LCM for a specified duration of time. For example, a 6 month completer cohort consists of subjects enrolled and treated with LCM for at least 6 months where a month is defined as 28 days.

Subjects will be classified as belonging to one or more of the following completer cohorts for the purpose of subgroup analyses:

- 6 months
- 12 months
- 24 months
- >24 months.

Has been changed to:

A completer cohort will be defined as the subset of subjects in the Full Analysis Set (FAS) that were enrolled, treated with LCM for a specified duration of time, and have efficacy data available for the duration of the cohort. For example, a 22-week completer cohort consists of subjects from the FAS, treated with LCM for at least 22 weeks and have efficacy data through at least 22 weeks of exposure.

Subjects will be classified as belonging to one or more of the following completer cohorts for the purpose of subgroup analyses:

- 22 weeks
- 46 weeks
- 94 weeks.

Section 3.2.3, Seizure cluster, was modified from:

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

Was changed to:

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

Section 3.3, Definition of Baseline values, the 2nd paragraph has been revised from:

For absence and myoclonic seizure data, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study.

Has been changed to:

For absence and myoclonic seizure data in order to determine Responder Status and worsening, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. In order to determine emergence of new seizure type, the Combined Baseline Period will be used.

Section 3.4, Protocol deviations, the section was changed from:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on either the primary efficacy or key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock to confirm exclusion from analysis sets.

Was changed to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

Section 4.2.1, Missing seizure diary days, this section has been revised from:

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

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

The calculation of average 28-day seizure frequency accounts for missing data in the first 2 years by only evaluating days for which data are available. A subject will only be considered seizure-free for absence or myoclonic seizures in the first 2 years if the subject had <10% of days during the time period being analyzed reported as “not done”. For years 3-5, when subjects are only required to enter days when seizures occur, days not reported are assumed to be seizure free.

Has been changed to:

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

For the purpose of the derivation of PGTC seizure-free status, in the first 2 years, if there are seizure counts reported as "not done" on a specific day, then the seizure count will be assumed to be zero on that date. For years 3-5, when subjects are only required to enter days when PGTCS occurred, days not reported are assumed to be PGTCS free; if seizure information is known to be missing, then the subject is not PGTCS free. The calculation of average 28-day PGTCS frequency accounts for missing data in the first 2 years by only evaluating days for which data are available. For years 3-5, the calculation of average 28-day PGTCS frequency uses the seizure information reported since "not done" information is no longer gathered; if there is a known non-compliance in recording seizures and the unevaluable days can be identified, then the average 28-day PGTCS frequency will use only evaluable days.

A subject will only be considered seizure-free for absence or myoclonic seizures in the first 2 years if the subject had <10% of days during the time period being analyzed reported as "not done". For years 3-5, when subjects are only required to enter days when absence or myoclonic seizures occur, days not reported are assumed to be seizure free.

Section 4.3, Interim analyses and data monitoring, this section was revised from:

No formal interim analysis is planned for this study. Interim data from EP0012 may be summarized to support a regulatory submission, regular safety signal detection monitoring, publications, and annual reports to regulatory agencies. For any interim data summaries, all available data as of the time of the database snapshot will be included. Subjects ongoing at the time of an interim data summary will be assumed to be treated up until the date of the clinical data cut-off. No Data Monitoring Committee is planned.

Has been changed to:

No formal interim analysis is planned for this study. Interim data from EP0012 may be summarized to support a regulatory submission, regular safety signal detection monitoring, publications, and annual reports to regulatory agencies. For any interim data summaries, all available data as of the time of the clinical cut-off date will be included. Subjects ongoing at the time of an interim data summary will be assumed to be treated up to and including the date of the clinical data cut-off. No Data Monitoring Committee is planned.

Section 4.8, Examination of subgroups, the Region subgroup was revised from:

- Region
  - North America: United States
  - Latin America: Brazil, Mexico
  - Western Europe: Belgium, France, Germany, Italy, Portugal, Spain
  - Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Turkey
  - Asia/Pacific/Other: Australia, Israel, Japan, South Korea, Taiwan.

Separate subgroupings are used for the purpose of summarizing the following scales:

Has been changed to:

- Region

- North America: United States, Puerto Rico
- Latin America: Brazil, Mexico
- Western/Central Europe: Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain
- Eastern Europe: Bulgaria, Romania, Russia, Turkey
- Asia/Pacific/Other: Australia, China, Israel, Japan, South Korea, Taiwan.

The following scales are assessed by specific age subgroupings. The following age subgroupings are used for the purpose of summarizing the following scales:

Section 6.2, Analysis of other Baseline Characteristics, the following was revised from:

- SP0982 exit status (Baseline failure, 24-week completer, met exit criteria).

Has been changed to:

- LCM study drug status (continuing LCM treatment (randomized to LCM in SP0982), new LCM treatment (randomized to PBO or baseline failure from SP0982))
- SP0982 exit status (Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up).

Section 6.4, Medical history and concomitant diseases, the first sentence was modified from:

Previous and ongoing medical history conditions will be summarized by system organ class (SOC) and preferred term (PT) for the SS.

Was changed to:

Previous and ongoing medical history conditions, initially reported in SP0982 and potentially updated for EP0012, will be summarized by system organ class (SOC) and preferred term (PT) for the SS.

Section 6.5, Prior and concomitant medications, the following sentence was added to the end of the first paragraph:

Prior AEDs, benzodiazepines and other medications are not summarized for the EP0012 subjects.

Section 8.2.2, Analysis of secondary efficacy variable, this section was revised from:

The percent change in PGTC seizure frequency during the Treatment Period by completer cohort will be summarized with descriptive statistics. The percent change in PGTC seizure frequency during the Treatment Period by completer cohort will also be summarized separately for subjects that are in the study for 1-2 years and subjects that are in the study for 3-5 years.

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

Has been changed to:

The percent change in PGTCS frequency during the Treatment Period by completer cohort will be summarized with descriptive statistics.

All PGTCS frequency per 28 days data will be listed.

Section 8.3.1.2, Variables: Responder status – reduction in PGTCS frequency, this section was revised from:

A responder is defined as a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from Combined Baseline to the period of interest. Response to treatment will be based on the percent change in seizure frequency, calculated as described in Section 8.2.1.

Has been changed to:

A 50% responder is defined as a subject experiencing ≥50% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest. Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1. A 75% responder is defined as a subject experiencing ≥75% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

Section 8.3.1.3, Variables: Responder status – reduction in days with absence seizures, this section was revised from:

A responder is defined as a subject experiencing ≥50% reduction in the number of days with absence seizures per 28 days from Prospective Baseline to the Treatment Period. Response to treatment will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1.

Has been changed to:

A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982. Response to treatment will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Section 8.3.1.4, Variables: Responder status – reduction in days with myoclonic seizures, this section was revised from:

A responder is defined as a subject experiencing ≥50% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline to the Treatment Period. Response to treatment will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1.

Has been changed to:

A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982. Response to treatment will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982.

Section 8.3.1.5, Variables: Seizure-free status, this section was revised from:

For years 1-2, the following definitions will be used:

A PGTC seizure-free day will be defined as a day where no PGTC seizures were reported in the seizure diary and seizures were assessed (ie, "no seizures" is marked or number is entered as zero). Days in the seizure diary which are marked as "not done" on the CRF will be counted as a PGTC seizure free day.

Seizure-free status will be determined for a particular time period. A subject will have PGTC seizure freedom (seizure free status=yes) for the time period if the subject completed the time period and reported "no seizures" or "not done" for all days during the time period.

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

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

For years 3-5, the following definitions will be used:

A PGTC seizure-free day will be defined as a day where no PGTC seizures were reported in the seizure diary.

Seizure-free status will be determined for a particular time period. A subject will have PGTC seizure freedom (seizure free status=yes) for the time period if the subject completed the time period and no seizures were reported during the time period.

A generalized seizure-free day will be defined as a day where no generalized seizures were reported in the seizure diary.

A subject will have seizure freedom (seizure free status=yes) for all generalized seizure types for the applicable time period if the subject completed the time period and reported zero generalized seizures during the time period.

Has been changed to:

For years 1-2, the following definitions will be used:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary and seizures were assessed (ie, "no seizures" is marked or number is entered as zero). Days in the seizure diary which are marked as "not done" on the CRF will be counted as a seizure-free day from PGTCS.

Seizure-free status will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and reported "no PGTC seizures" or "not done" for all days during the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary and seizures were assessed. Days in

the seizure diary which are marked as “not done” on the CRF will not be counted as a seizure free day.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero generalized seizures for all days during the time period when the number of generalized seizures was available, and had <10% of days during the time period with seizure data reported as “not done”.

For years 3-5, the following definitions will be used:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary.

Seizure-free status from PGTCS will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and no PGTCS were reported during the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero seizures during the time period.

Section 8.3.1.6, Variable: Worsening of PGTCS, this section was added:

Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1. Seizure worsening is defined as a subject experiencing ≥50% increase in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

Section 8.3.1.7, Variable: Worsening of days with absence seizures, this section was added:

Response to treatment will be based on the percent change in days with absence seizures, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Section 8.3.1.8, Variable: Worsening of days with myoclonic seizures, this section was added:

Response to treatment will be based on the percent change in days with myoclonic seizures, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982.

Section 8.3.2.2, Analysis: Responder status – reduction in PGTCS frequency, this was revised from:

The number and percentage of responders will be summarized for the Treatment Period with descriptive statistics.

Has been changed to:

The number and percentage of ≥50% and ≥75% responders will be summarized by completer cohort and Treatment Period.

Section 8.3.2.3, Analysis: Responder status – reduction in days with absence seizures, this was revised from:

The number and percentage of responders will be summarized for the Treatment Period with descriptive statistics.

Has been changed to:

The number and percentage of ≥50% and ≥75% responders will be summarized by completer cohort and Treatment Period.

Section 8.3.2.4, Analysis: Responder status – reduction in days with myoclonic seizures, this was revised from:

The number and percentage of responders will be summarized for the Treatment Period with descriptive statistics.

Has been changed to:

The number and percentage of ≥50% and ≥75% responders will be summarized by completer cohort and Treatment Period.

Section 8.3.2.5, Analysis: Seizure-free status, this was revised from:

The number and percentage of subjects with seizure-free status (yes/no) will be summarized by completer cohort for the following types of seizures:

- Seizure-free status (yes, no) for PGTC seizures
- Seizure-free status (yes, no) for all generalized seizure types

Has been changed to:

The number and percentage of subjects with seizure-free status (yes/no) will be summarized by completer cohort and Treatment Period for the following types of seizures:

- Seizure-free status (yes, no) for PGTCS
- Seizure-free status (yes, no) for all generalized seizure types.

Section 8.3.2.6, Analysis: PGTCS worsening, this section was added:

The number and percentage of subjects with seizure worsening, ≥50% increase in PGTCS frequency per 28 days, will be summarized by completer cohort and Treatment Period.

Section 8.3.2.7, Analysis: Worsening in days with absence seizures, this section was added:

The number and percentage of subject with ≥50% increase in days with absence seizures per 28 days will be summarized by completer cohort and Treatment Period.

Section 8.3.2.8, Analysis: Worsening in days with myoclonic seizures, this section was added:

The number and percentage of subjects with ≥50% increase in days with myoclonic seizures per 28 days will be summarized by completer cohort and Treatment Period.

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

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

Section 8.4.2.1, QOLIE-31-P variables, the following sentence was added at the end of this section:

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

Section 8.4.2.2, PedsQL variables, the following sentence was added at the end of this section:

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

Section 8.4.2.3, EQ-5D-3L quality of life variables, the following was added at the end of this section:

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

Section 10.1.2, Analysis of exposure variables, the 2nd bullet point was revised from:

- Number and percentage of subjects within each LCM treatment duration category by modal dose and maximum daily dose. LCM treatment duration categories (days) are as follows: 1 to 84; 85 to 168; 169 to 336; 337 to 504; 505 to 672; 673 to 1008; 1009 to 1344; 1345 to 1680; >1680; any duration (total of durations)

Has been changed to:

- Number and percentage of subjects within each LCM treatment duration category by modal dose and maximum daily dose. LCM treatment duration categories (days) are as follows: 1 to 84; 85 to 168; 169 to 336; 337 to 504; 505 to 672; 673 to 1008; 1009 to 1344; 1345 to 1680; >1680; any duration (total of durations). The LCM dose categories for oral solution are as follows: 0mg/kg/day/Unknown, >0 to <4mg/kg/day, ≥4mg/kg/day to <8mg/kg/day, and ≥8mg/kg day. The LCM dose categories for tables are as follows: 0mg/day/Unknown, >0 to <200mg/day, ≥200 to <400mg/day, ≥400 to <600mg/day, ≥600 to 800mg/day, and ≥800mg/day.

Section 10.2, Adverse events, has been revised from:

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

Adverse events will be considered treatment-emergent if the event had onset on or after the date of the first study medication dose in EP0012 and within 30 days following the last study medication dose or events whose intensity worsened on or after the date of first study medication dose and within 30 days following the date of last study medication administration.

If the last dose of study medication administration is unknown, any event occurring after the first study medication dose will be considered treatment-emergent. If the start date of an AE is

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

Only TEAEs that start on or after the date of Visit 1 will be summarized in tables i.e. ongoing AEs from the SP0982 study will not be considered treatment emergent. AEs that start in SP0982 but worsen in EP0012 will be recorded in the EP0012 database with a new start date.

The following summaries will be presented:

- Overview of TEAEs
- Overview of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs
- Incidence of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs by intensity
- Incidence of TEAEs by relationship
- Incidence of serious TEAEs
- Incidence of serious TEAEs– Subject numbers
- Incidence of TEAEs leading to discontinuation
- Incidence in TEAEs leading to discontinuation– Subject numbers
- Incidence of other significant TEAEs (See Section 11.2 for details)
- Incidence of TEAEs by 100 person-months of exposure during the study

The following summaries will be presented by dose at onset (Unknown/Missed, >0 to <4mg/kg/day, ≥4 to <8mg/kg/day, ≥8 to <12mg/kg/day and ≥12mg/kg/day, >0 to <200mg/day, ≥200 to <300mg/day, ≥300 to <400mg/day, and ≥400mg/day). Adverse events of unknown dosing are not summarized but those taken where LCM dose is 0mg/kg/day or 0mg/day are in the applicable column. Adverse events of unknown dosing are those with UNK as the dose or known dosing and partial AE start or stop dates.

- Incidence of TEAEs by dose at onset
- Incidence of Serious TEAEs by dose at onset
- Incidence of TEAEs leading to discontinuation by dose at onset

Subject data listings will be presented for the following:

- Subjects experiencing TEAEs
- Subjects experiencing serious TEAEs
- Subjects experiencing TEAEs leading to discontinuation

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

A list of further AE tables required for EudraCT and clinicaltrials.gov is provided in Section 11.5.

Has been changed to:

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

Adverse events will be considered treatment-emergent if the event had onset on or after the date of the first study medication dose in EP0012 and within 30 days following the last study medication dose or events whose intensity worsened on or after the date of first study medication dose and within 30 days following the date of last study medication administration.

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

Only TEAEs that start on or after the date of Visit 1 will be summarized in tables (ie, ongoing AEs from the SP0982 study will not be considered treatment emergent). AEs that start in SP0982 but worsen in EP0012 will be recorded in the EP0012 database with a new start date.

The following summaries will be presented:

- Overview of TEAEs
- Overview of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs
- Incidence of TEAEs by subgroup as detailed in Section 4.8
- Incidence of TEAEs by intensity
- Incidence of TEAEs by relationship
- Incidence of serious TEAEs
- Incidence of serious TEAEs – Subject numbers
- Incidence of TEAEs leading to discontinuation
- Incidence in TEAEs leading to discontinuation – Subject numbers
- Incidence of other significant TEAEs (See Section 11.2 for details)
- Incidence of TEAEs for potential drug-induced liver injury (PDILI) (See Section 11.2 for details)
- Incidence of TEAEs by 100 person-months of exposure during the study
- Incidence of TEAEs by 3-month exposure period of TEAE onset

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

The 100 person-months of exposure calculation takes the incidence of subjects with TEAEs, divides it by the total exposure and multiplies by 100.

To assess TEAEs related to epilepsy, PTs will be identified by ongoing manual medical review. The following PTs (including those identified from continuing medical review) will be summarized by 3-month periods of TEAE onset: petit mal epilepsy, myoclonus, and myoclonic epilepsy.

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

- Incidence of TEAEs by dose at onset
- Incidence of Serious TEAEs by dose at onset
- Incidence of TEAEs leading to discontinuation by dose at onset

Subject data listings will be presented for the following:

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

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

A list of further AE tables required for EudraCT and clinicaltrials.gov is provided in Section 11.5.

Section 10.3, Clinical laboratory evaluations, this section has been revised from:

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

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

Markedly abnormal (MA) values indicate significant deviations from the expected range of age-appropriate values. Marked laboratory abnormalities observed post-Baseline during the

Treatment Period but not present at Baseline are considered treatment emergent. Markedly abnormal values for serum chemistry and hematology laboratory parameters are provided in UCB conventional (traditional) and standard units. The definition of MA values for hematology and chemistry values can be found in Section 11.3.

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

The National Cancer Institute common toxicity criteria (NCI CTC) can be found in Section 11.4. The number and percentage of subjects with treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher (hematology and clinical chemistry) will be summarized by laboratory parameter, and visit for the Treatment Period. Treatment emergent abnormalities of grade 2 or higher are those that were observed during the Treatment Period at scheduled visits and not reporting a grade 2 or higher abnormality during the Baseline Period.

Subject data listings of all laboratory data will also be presented.

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

Has been changed to:

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

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

Treatment-emergent markedly abnormal (TEMA) values indicate significant deviations from the expected range of age-appropriate values. TEMA laboratory results are those that are observed post-Baseline during the Treatment Period but not present at Baseline. TEMA values for serum chemistry and hematology laboratory parameters are provided in UCB conventional (traditional) and standard units. The definition of TEMA values for hematology and chemistry values can be found in Section 11.3. The number and percentage of subjects with at least 1 TEMA value will be presented by scheduled visit, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified.

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

The National Cancer Institute common toxicity criteria (NCI CTC) can be found in Section 11.4. The number and percentage of subjects with treatment emergent laboratory abnormalities of NCI

CTC grade 2 or higher (hematology and clinical chemistry) will be summarized by laboratory parameter, and visit for the Treatment Period. Treatment emergent abnormalities of grade 2 or higher are those that were observed during the Treatment Period at scheduled visits and not reporting a grade 2 or higher abnormality during the Baseline Period. All treatment emergent laboratory abnormalities of NCI CTC grade 2 or higher will be presented in a subject number listing.

Subject data listings of all laboratory data will also be presented.

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

Section 10.4.1, Vital signs, the 2nd paragraph has been revised from:

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value, at each post-Baseline visit up to Visit 10, for which SBP, DBP and pulse rate were scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects with a value at each time point. The abnormal vital sign criteria are defined in Section 11.3.3.

Has been changed to:

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value, at each post-Baseline visit up to Visit 10, for which SBP, DBP and pulse rate were scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects with a value at each time point. All TEMA results summarized will be presented in a subject number listing. The abnormal vital sign criteria are defined in Section 11.3.3.

Section 10.4.2.2, Analysis of ECG parameters, this section has been revised from:

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

The number and percentage of subjects with QT interval values classified as <450ms, 450 to <480ms, 480 to <500ms and ≥500ms and an increase from Baseline of <30ms, 30 to <60ms and ≥60ms will be summarized for uncorrected QT, QTcB, and QTcF by visit.

The number and percentage of subjects who met each of the criteria specified in Section 11.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval and QRS interval.

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

Has been changed to:

For quantitative ECG measurements (heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT intervals using Bazett and Fridiricia correction methods), summary statistics of the actual values and change from Baseline (where Baseline is from SP0982 as defined in Section 0) will be summarized for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the TEMA ECG criteria age categories. Last visit is the value from the last post-baseline visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values are listed.

The number and percentage of subjects who met each of the TEMA criteria specified in Section 11.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval, QRS interval, QT interval and corrected QT intervals by scheduled visits and Last Visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by visit summaries, but will be considered when determining the last visit values during the Treatment Period. Subject numbers for those with TEMA ECG values will be listed by abnormality criteria.

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

Section 10.4.7.2, Analysis of Achenbach variables, the following sentence was added to the end of this section:

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

Section 10.4.8.1, BRIEF-P scores, the following sentence was added to the end of this section:

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

Section 10.4.8.2, BRIEF scores, the following sentence was added to the end of this section:

The means of the BRIEF assessment data will be plotted.

Section 10.4.9, Safety Seizure Information, this section changed from:

10.4.9.1 New Seizure Type

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

10.4.9.2 Increase in days with absence seizures

Response to treatment regarding absence seizures will be based on the percent change in the number of days with absence seizures per 28 days for the first 2 years of treatment, calculated as described in Section 8.3.1.1. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with absence seizures per 28 days during the first 2 years of the Treatment Period compared to the Prospective Baseline will be presented.

10.4.9.3 Increase in days with myoclonic seizures

Response to treatment regarding myoclonic seizures will be based on the percent change in the number of days with myoclonic seizures per 28 days for the first 2 years of treatment, calculated as described in Section 8.3.1.1. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with myoclonic seizures per 28 days during the first 2 years of the Treatment Period compared to the Prospective Baseline will be presented.

Has been changed to:

10.4.9.1 New Seizure Type or Worsening Over Time

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period with absence or myoclonic, respectively, indicated by the Seizure History Classification, but not experienced in the Combined Baseline Period, as recorded in the diary, will be summarized overall and by LCM study drug status by 1-month period of seizure onset.

The number and percentage of subjects with new absence or myoclonic seizure types experienced in the Treatment Period but not experienced in Combined Baseline Period or in seizure classification history, as recorded in the diary, will be summarized overall and by LCM study drug status by 1-month period of seizure onset.

The number and percentage of subjects with new absence or myoclonic seizures in the Treatment Period, with absence or myoclonic, respectively, indicated by the Seizure History Classification but not experienced in the Combined Baseline Period as recorded in the diary in subjects with a history of absence or myoclonic seizures, respectively, or subjects with ≥50% increase in days with absence or myoclonic seizures, respectively, per 28 days as compared to Prospective Baseline (for those subjects with absence or myoclonic seizure data, respectively, reported in the Prospective Baseline Period in SP0982), will be summarized overall and by LCM study drug status by 1 month period of seizure onset.

The number and percentage of subjects with ≥50% increase in days in absence or myoclonic seizures as compared to Prospective Baseline Period (for those subjects with absence or myoclonic seizure data, respectively, reported in the Prospective Baseline Period in SP0982), will be summarized by 1-month period of seizure onset.

10.4.9.2 Increase in days with absence seizures

Response to treatment regarding absence seizures will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the number of days with absence seizures per 28 days during the Treatment Period compared to the Prospective Baseline Period (for those subjects with absence seizure data reported in the Prospective Baseline Period in SP0982) will be presented.

10.4.9.3 Increase in days with myoclonic seizures

Response to treatment regarding myoclonic seizures will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1. The number and percentage of subjects experiencing an increase of up to 25%, >25% to 50%,

>50% to 75%, and >75% in the number of days with myoclonic seizures per 28 days during the Treatment Period compared to the Prospective Baseline Period (for those subjects with myoclonic seizure data reported in the Prospective Baseline Period in SP0982) will be presented.

Section 11.2.1, List of other significant AEs, this table has been updated.

Section 11.2.2, List of AEs for potentially drug induced liver injury, this table has been added.

Section 11.3.4, ECG Abnormality Criteria, some of the criteria have been updated.

Section 11.5, Appendix 5, the table titles have been updated in this section.

Section 11.6, the section has been added.

12.2 Amendment 2

12.2.1 Rationale for the amendment

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

12.2.2 Modification and changes

- Analyses involving post-treatment vital sign and QTc measurements were added

The following item was clarified:

- Algorithm for identifying rescue medications

The following items were added:

- An analysis of subjects withdrawing from background AEDs to monotherapy with LCM
- A new listing of rescue medications
- New variable identifying Asian sites

12.2.2.1 Specific changes

The information below was revised from:

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018

Has been revised to:

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018
SAP Amendment #2	10 Oct 2019

Section 3.1, General presentation of summaries and analyses, the following text was added to the end of the section:

Efficacy analyses will be performed on data reported during analysis treatment period. PGTCS analyses will be done on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 days, any PGTCS reported during the gap will not be included in PGTCS summaries. Safety analyses will be performed on data reported during the analysis treatment period. All data reported in the study will be listed in subject data listings.

Section 3.2.1.5, Completer cohorts, the following sentence was modified from:

A completer cohort will be defined as the subset of subjects in the Full Analysis Set (FAS) that were enrolled, treated with LCM for a specified duration of time, and have efficacy data available for the duration of the cohort.

Was revised to:

A completer cohort will be defined as the subset of subjects in the Full Analysis Set (FAS) that were enrolled, treated with LCM for the specified duration of time (allowing gaps of 3 days or less), and have efficacy data available for the duration of the cohort.

Section 3.2.1.6, Time Period, the following section was added:

The time periods for the Treatment Period seizure analysis are “0 to 22 Weeks”, “>22 to 46 Weeks”, “>46 to 94 Weeks”, “>94 to 142 Weeks”, “>142 to 190 Weeks”, “>190 to 238 Weeks”, “0 to 46 Weeks”, “0 to 46 Weeks (> 22 Weeks)”, “0 to 94 Weeks”, “0 to 94 Weeks (> 46 Weeks)”, “0 to 142 Weeks”, “0 to 142 Weeks (>94 Weeks)”, “0 to 190 Weeks”, and “0 to 238 Weeks”. Additional time periods will be added based on the visit schedule as subjects progress through the study.

The time periods include all data in the time window of the time period of interest including early termination and end of taper visit data. A calculation may be needed using dates to determine what time period the early termination and end of taper visit data fit into for each subject.

Section 3.2.4, the following text was changed from:

Antiepileptic drugs (AEDs) and benzodiazepines will be collected on the concomitant and prior medication case report form (CRF) for AEDs. New concomitant AEDs can be added at any time. Stable use of benzodiazepines is allowed as concomitant AEDs. Intermittent use of

benzodiazepines is allowed as rescue medication for epilepsy indications with a maximum of 1 dose per week. Benzodiazepines used as rescue medication will be flagged with "RESCUE" in the indication field on the CRF. Rescue benzodiazepines will also be identified programmatically as any benzodiazepines taken intermittently as 1 dose per week.

Was revised to:

Antiepileptic drugs (AEDs) and benzodiazepines will be collected on the concomitant and prior medication case report form (CRF) for AEDs. New concomitant AEDs can be added at any time. Stable use of benzodiazepines is allowed as concomitant AEDs. Intermittent use of

benzodiazepines is allowed as rescue medication for epilepsy indications with a maximum of 1 dose per week. Benzodiazepines used as rescue medication will be flagged with "RESCUE" in the indication field on the CRF. Rescue AEDs will also be identified programmatically as any AED with an epilepsy or seizure related indication taken intermittently as 1 dose per week.

Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to Visit 1.

Section 4.2, Handling of dropouts or missing data, the following text was added to the beginning of the section:

For subjects missing data at the first visit in EP0012, data from SP0982 will be checked as follow:

- for subjects who transitioned from SP0982 to EP0012, final clinic visit data in SP0982 will be checked for data not reported for V1 in EP0012.
- for subjects who are baseline failures or incomplete screen failures in SP0982 who enrolled in EP0012, baseline data will be used from EP0012 V1 (if prior to first EP0012 dose) or the latest data from the screening and baseline visits in SP0982 can be used (also if prior to first EP0012 dose).

Section 4.2.1, Missing seizure diary days, the following text was changed from:

A subject will only be considered seizure-free for absence or myoclonic seizures in the first 2 years if the subject had <10% of days during the time period being analyzed reported as "not done". For years 3-5, when subjects are only required to enter days when absence or myoclonic seizures occur, days not reported are assumed to be seizure free.

Was revised to:

For all seizure types, any missing day in the seizure diary during years 1-2 renders a subject to be not seizure-free due to the lack of information.

Absence or myoclonic subjects will be considered for seizure-free evaluation from all generalized seizure types in years 1-2 for the applicable time period if the subject had <10% of days during the time period with seizure data reported as "not done".

For years 3-5, when subjects are only required to enter days when generalized seizures occur, a subject will be considered seizure-free for generalized seizures if the subject has no days reported with generalized seizures (seizure type=II).

Section 4.9, Data Handling Method of Textual Results in Laboratory Data, the following section was added:

For laboratory data analysis, any textual data above the upper LOQ (eg. ">n.nnn") will be set to the upper LOQ and used when determining the maximum.

The original value will be displayed in subject data listings.

Section 6.2.2, Analysis of other Baseline characteristics, the following text was changed from:

- SP0982 exit status (Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up).

Was revised to:

- SP0982 exit status (Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up, SP0982 early discontinuation).

Section 6.5, Prior and concomitant medications, the following text was added to the end of the section:

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

The number of subjects withdrawing to Monotherapy during the Treatment Period will be summarized. Withdrawing to monotherapy means the subject has documentation that all background AEDs [except LCM] were discontinued during Treatment Period) will be summarized. A record for the discontinued AED must be present in the concomitant AED data.

Section 8. Efficacy Analyses, the following text was changed from:

Analyses of the efficacy variables will be performed using the FAS and will be descriptive in manner only.

All seizure diary data will be listed. A listing of subjects excluded from the FAS will also be produced.

Was revised to:

Analyses of the efficacy variables will be performed using the FAS (unless otherwise stated) and will be descriptive in manner only. Efficacy analyses will be performed on data reported during analysis treatment period. PGTCS analyses will be done on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 days, any PGTCS reported during the gap will not be included in PGTCS summaries.

All seizure diary data will be listed. A listing of subjects excluded from the FAS will also be produced.

Section 8.2.2 Analysis of secondary efficacy variable, the following text was changed from:

The percent change in PGTCS frequency during the Treatment Period by completer cohort will be summarized with descriptive statistics.

All PGTCS frequency per 28 days data will be listed.

Was revised to:

The percent change in PGTCS frequency during the Treatment Period by Completer Cohort and Time Period will be summarized with descriptive statistics.

The percent change in PGTCS frequency over the Treatment Period by Time Period will be summarized with descriptive statistics.

All PGTCS frequency per 28 days data will be listed.

Section 8.3, Analysis of seizure related other efficacy variables, the following text was added to the beginning of the section:

All seizure data recorded during the treatment period will be summarized and listed for the seizure related other efficacy variables.

For absence seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of absence seizures or reported absence seizures during baseline or the treatment period.

For myoclonic seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of myoclonic seizures or reported myoclonic seizures during baseline or the treatment period.

Section 8.3.1.5 Variables: Seizure-free status, the following text was added:

For all seizure types, any missing day in the seizure diary during years 1-2 renders a subject to be not seizure-free due to the lack of information.

Section 8.3.1.5 Variables: Seizure-free status, the following text was changed from:

Seizure-free status will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and reported "no PGTC seizures" or "not done" for all days during the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary and seizures were assessed. Days in the seizure diary which are marked as "not done" on the CRF will not be counted as a seizure free day.

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

For years 3-5, the following definitions will be used:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary.

Seizure-free status from PGTCS will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and no PGTCS were reported during the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero seizures during the time period.

Was revised to:

PGTCS free status will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and reported only a combination of "no PGTC seizures" or "not done" for all days during the time period. If 1 or more PGTCS are reported in the time period or if the seizure data is missing, then the subject does not have PGTCS free status=Yes for the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary and seizures were assessed. An absence or myoclonic subject will be considered for seizure-free evaluation for generalized seizure-free status in years 1-2 for the applicable time period if the subject had <10% of days during the time period with seizure data reported as "not done". If 1 or more seizure type=II seizures are reported in the time period, if there is missing data or if there are 10% or more "Not done" days for an absence and/or myoclonic seizure subject, then the subject does not have generalized seizure-free status=Yes for the time period.

For years 3-5, the following definitions will be used:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary.

Seizure-free status from PGTCS will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and no PGTCS were reported during the time period. If 1 or more PGTCS are reported in the time period, then the subject does not have PGTC seizure-free status=Yes for the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero seizure type=II seizures during the time period. If 1 or more seizure type=II seizures are reported in the time period, then the subject does not have generalized seizure-free status=Yes for the time period.

Section 8.3.1.7 Variable: Worsening of days with absence seizures, the following text was changed from:

Response to treatment will be based on the percent change in days with absence seizures, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Was revised to:

Response to treatment will be based on the percent change in days with absence seizures per 28 days, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with absence seizures per 28 days from Prospective Baseline Period to the

period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

The increase in days with absence seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Section 8.3.1.8 Variable: Worsening of days with myoclonic seizures, the following text was changed from:

Response to treatment will be based on the percent change in days with myoclonic seizures, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982.

Was revised to:

Response to treatment will be based on the percent change in days with myoclonic seizures per 28 days, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982.

The increase in days with myoclonic seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982.

Section 8.3.2 Analysis of seizure-related other efficacy variables – throughout this section, it was clarified which analysis would be performed on the SS.

Section 8.3.2.1 Analysis: Days with seizures per 28 days, the following text was changed from:

The following data will be summarized with descriptive statistics only:

- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and completer cohort
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and completer cohort
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and completer cohort
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and completer cohort.

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

Was revised to:

The following data will be summarized with descriptive statistics only:

- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort

- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Time Period
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Time Period
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Time Period
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort.
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Time Period

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

Section 8.3.2.2 Analysis: Responder status – reduction in PGTCS frequency, the following text was changed from:

The number and percentage of ≥50% and ≥75% responders will be summarized by completer cohort and Treatment Period.

Was revised to:

The number and percentage of ≥50% and ≥75% responders will be summarized Time Period and Treatment Period.

Section 8.3.2.3Analysis: Responder status – reduction in days with absence seizures, the following text was changed from:

The number and percentage of ≥50% and ≥75% responders will be summarized by completer cohort and Treatment Period.

Was revised to:

The number and percentage of ≥50% and ≥75% responders will be summarized by Time Period and Treatment Period.

Section 8.3.2.4 Analysis: Responder status – reduction in days with myoclonic seizures, the following text was changed from:

The number and percentage of ≥50% and ≥75% responders will be summarized by completer cohort and Treatment Period.

Was revised to:

The number and percentage of ≥50% and ≥75% responders will be summarized by Time Period and Treatment Period.

Section 8.3.2.6 Analysis: PGTCS worsening, the following text was changed from:

The number and percentage of subjects with seizure worsening, ≥50% increase in PGTCS frequency per 28 days, will be summarized by completer cohort and Treatment Period.

Was revised to:

The number and percentage of subjects with seizure worsening, ≥50% increase in PGTCS frequency per 28 days, will be summarized by Time Period and Treatment Period.

Section 8.3.2.7Analysis: Worsening in days with absence seizures, the following text was changed from:

The number and percentage of subject with ≥50% increase in days with absence seizures per 28 days will be summarized by completer cohort and Treatment Period.

Was revised to:

The number and percentage of subject with ≥50% increase in days with absence seizures per 28 days will be summarized by Time Period and Treatment Period.

Section 8.3.2.8 Analysis: Worsening in days with myoclonic seizures, the following text was changed from:

The number and percentage of subjects with ≥50% increase in days with myoclonic seizures per 28 days will be summarized by completer cohort and Treatment Period.

Was revised to:

The number and percentage of subject with ≥50% increase in days with myoclonic seizures per 28 days will be summarized by Time Period and Treatment Period.

Section 10.2 Adverse events, the following rest was changed from:

The 100 person-months of exposure calculation takes the incidence of subjects with TEAEs, divides it by the total exposure and multiplies by 100.

Was revised to:

The 100 person-months of exposure calculation takes the incidence of subjects with TEAEs, divides it by the total exposure in months and multiplies by 100. Exposure in days is divided by 28 days to get exposure in months.

Section 10.3 Clinical laboratory evaluations, the following text was changed from:

The definition of TEMA values for hematology and chemistry values can be found in Section 11.3. The number and percentage of subjects with at least 1 TEMA value will be presented by scheduled visit, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified.

Was revised to:

The definition of TEMA values for hematology and chemistry values can be found in Section 11.3. The number and percentage of subjects with at least 1 TEMA value will be presented by scheduled visit, Last Visit, Early Termination Visit, minimum and maximum post-Baseline values obtained during the Treatment Period for each laboratory parameter (hematology and clinical chemistry) with markedly abnormal criteria specified. A subject can be summarized

in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg, Pediatric subjects) for the markedly abnormal criteria.

Section 10.4 Vital signs, physical findings, and other observations related to safety, the following text was changed from:

The number and percentage of subjects with a TEMA value, TEMA low value, and TEMA high value, at each post-Baseline visit up to Visit 10, for which SBP, DBP and pulse rate were scheduled to be assessed, and Last Visit, will be presented. Percentages will be relative to the number of subjects with a value at each time point. All TEMA results summarized will be presented in a subject number listing. The abnormal vital sign criteria are defined in Section 11.3.3.

Was revised to:

The number and percentage of subjects with at least 1 TEMA value will be presented at each post-Baseline visit, Last Visit, Early Termination Visit and minimum and maximum post-Baseline values obtained during the Treatment Period. Percentages will be relative to the number of subjects with a value at each time point.

A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg. Pediatric subjects) for the TEMA criteria.

Section 10.4.2.2 Analysis of ECG parameters, the following text was changed from:

The number and percentage of subjects who met each of the TEMA criteria specified in Section 11.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval, QRS interval, QT interval and corrected QT intervals by scheduled visits and Last Visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by visit summaries, but will be considered when determining the last visit values during the Treatment Period. Subject numbers for those with TEMA ECG values will be listed by abnormality criteria.

Was revised to:

The number and percentage of subjects who met each of the TEMA criteria specified in Section 11.3.4 will be presented within the specified age groups. For each parameter, the number and percentage of subjects with an abnormality (ie subjects who met any of the criteria specific to their age) will be summarized for heart rate, PR interval, QRS interval, QT interval and corrected QT intervals by scheduled visits and Last Visit, Early Termination Visit, minimum and maximum post-Baseline values obtained during the Treatment Period. A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg, Pediatric subjects) for the TEMA criteria.

Repeated or unscheduled ECG assessments during the study will not be presented in by visit summaries, but will be considered when determining the last visit values during the Treatment Period. Subject numbers for those with TEMA ECG values will be listed by abnormality criteria.

The number and percentage of subjects with QT interval values classified as <450ms, 450 to <480ms, 480 to <500ms and ≥500ms and an increase from Baseline of <30ms, 30 to <60ms and ≥60ms will be summarized for uncorrected QT, QTcB, and QTcF by visit.

Section 10.4.8.2 BRIEF scores, Table 4, question 28 was added to the list of items used for scoring of Plan/Organize individual component score

Section 11.3.1 Hematology, the following table was changed from:

Table 12 Hematology Markedly Abnormal Values

Parameter	UNIT (conventional)	abnormality Criteria (conventional unit)	unit (standard)	Abnormality Criteria (standard unit)
Hematocrit	%	≤85% of LLN ≥115% of ULN	%	≤85% of LLN ≥115% of ULN
Hemoglobin	g/dL	≤85% of LLN ≥115% of ULN	g/L	≤85% of LLN ≥115% of ULN
WBC/Leukocytes	10^9/L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0
Platelets	10^9/L	≤100 ≥600	G/L	≤100 ≥600
RBC/ Erythrocytes	10^{12}/L	<3.5	T/L	<3.5

Abbreviations: LLN=lower limit of normal, ULN=upper limit of normal.

Was revised to:

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

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

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

Section 11.3.2 Chemistry, the following table was changed from:

Table 13 Chemistry - Markedly Abnormal Values

Parameter	***UNIT (conventional)***	***Abnormality Criteria (conventional)***	***Unit (standard)***	***Abnormality Criteria (standard)***
AST (SGOT)	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)	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	U/L	≥3.0 x ULN	U/L	≥3.0 x ULN
GGT	U/L	≥3.0 x ULN	U/L	≥3.0 x ULN
Total Bilirubin	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	g/dL	<4.3 >13.0	g/L	<43 >130
Albumin	g/dL	<2.6	g/L	<26
BUN	mg/dL	≥40	mmol/L	≥14.28
Creatinine	mg/dL	≥2.0	umol/L	≥176.8
Creatinine Clearance*	mL/min	<50	mL/s	<0.835
Bicarbonate	mEq/L	<18 >38	mmol/L	<18 >38
Calcium	mg/dL	≤7.6 ≥11.0	mmol/L	≤1.9 ≥2.75
Chloride	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112

Parameter	***UNIT (conventional)***	***Abnormality Criteria (conventional)***	***Unit (standard)***	***Abnormality Criteria (standard)***
Phosphorous	mg/dL	≤2.0 ≥6.0	mmol/L	≤0.646 ≥1.938
Potassium	mEq/L	≤3.0 ≥6.0	mmol/L	≤3.0 ≥6.0
Sodium	mEq/L	<127 >151	mmol/L	<127 >151
Glucose	mg/dL	<50 ≥200	mmol/L	<2.775 ≥11.1
Uric Acid	mg/dL	>9.5	umol/L	>565.06

Abbreviations: ALT=alanine aminotransferase; AS =aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; ULN=upper limit of normal;

*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.

Was revised to:

Parameter	**Age Range**	**UNIT** (conventional)	**abnormality Criteria** (conventional)	**unit** (standard)	**Abnormality Criteria** (standard)
AST (SGOT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
Alkaline Phosphatase	4y - <10y	U/L	≥834	U/L	≥834
	10y - <17y		≥1761		≥1761
	≥17y		≥3.0 x ULN		≥3.0 x ULN
GGT	1y - <13y	U/L	≥66	U/L	≥66
	13y - <17y		≥126		≥126
	≥17y		≥3.0 x ULN		≥3.0 x ULN
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	1y - <17y	g/dL	<4.3 >12.0	g/L	<43 >120
	≥17y		<4.3 >13.0		<43 >130
Albumin	≥1y - <17y	g/dL	<2.4 >8.4	g/L	<24 >84
	≥17y		<2.6		<26
BUN	1y - <17y	mg/dL	≥36	mmol/L	≥12.852
	≥17y		≥40		≥14.28
Urea	≥1y	mg/dL	>60	mmol/L	>10.02
Creatinine	1y - <10y	mg/dL	>1.2	umol/L	>106.8
	10y - <16y		>1.8		>159.12
	≥16y		≥2.0		≥176.8
Creatinine Clearance*	All	mL/min	<50	mL/s	<0.835

Parameter	**Age Range**	**UNIT** (conventional)	**abnormality Criteria** (conventional)	**unit** (standard)	**Abnormality Criteria** (standard)
Bicarbonate	>1m - <17y	mEq/L	<15 >38	mmol/L	<15 >38
	⩾17y		<18 >38		<18 >38
Calcium	1y - <17y	mg/dL	<7.4 >11.7	mmol/L	<1.85 >2.925
	⩾17y		⩽7.6 ⩾11.0		⩽1.9 ⩾2.75
Chloride	>1m	mEq/L	≤90 ≥112	mmol/L	≤90 ≥112
Phosphorous	1y - <17y	mg/dL	<1.8 >7.4	mmol/L	<0.5814 >2.3902
	⩾17y		⩽2.0 ⩾6.0		⩽0.646 ⩾1.938
Potassium	⩾1y	mEq/L	⩽3.0 ⩾6.0	mmol/L	⩽3.0 ⩾6.0
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151
Glucose	>1m - <17y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99
	⩾17y		<50 ⩾200		<2.775 ⩾11.1
Total Cholesterol	≥1y	mg/dL	>250	mmol/L	>6.475
LDL (calculated)	1y - <17y	mg/dL	>140	mmol/L	>3.626
	⩾17y		>200		>5.18
HDL	>2y	mg/dL	<20	mmol/L	<0.518
Triglycerides	⩾1y	mg/dL	>300	mmol/L	>3.39
Uric Acid	1y - <13y	mg/dL	>6.5	umol/L	>386.62
	13y - <17y		>8.6		>511.528
	⩾17y		>9.5		>565.06
Thyroxine (T4)	⩾1y	ug/dL	⩽3.8 ⩾13.5	nmol/L	⩽48.9098 ⩾173.7585
Globulin	⩾1y	g/dL	<1.2 >5.3	g/L	<12 >53

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; GGT: gamma-glutamyltransferase; L = liter; LLN = lower limit of normal; m = month; mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = year.

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

Section 11.3.3 Vital signs, the following table was changed from:

Table 14 Vital Signs Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	3y - <12y	<50 >80
	12y - <17y	≤50 ≥105
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥105 and an increase from Baseline of ≥ 15

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

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

Was revised to:

Table 15 Vital Signs Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	3y - <12y	<60 >130
	12y - <17y	≤50 ≥120
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥120 and an increase from Baseline of ≥15 <60[a] >100[a]
Systolic Blood Pressure (mmHg)	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥180 and an increase from Baseline of ≥20 <90[a] >140[a] >160[a]
Diastolic Blood Pressure (mmHg)	3y - <12y	<50 >80
	12y - <17y	≤50 ≥105
	≥17y	≤50 and a decrease from Baseline of ≥15 ≥105 and an increase from Baseline of ≥ 15 <50[a] >90[a] >100[a]

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)[ba] ≥7% change from Baseline (an increase or a decrease)[a]

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

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

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

Section 11.3.4 ECG, the following table was changed from:

Table 16 ECGs Abnormality Criteria

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	≥500
	≥12y	<450, 450-<480, 480-<500, ≥500 or <30, 30-<60, ≥60 increase from Baseline
QTc(F) (ms)	3y-<12y	>440, or >15% increase from Baseline
	≥12y- <17y	>440, or >15% increase from Baseline
	≥17y	<450, 450-<480, 480-<500, ≥500 or <30, 30-<60, ≥60 increase from Baseline
QTc(B) (ms)	3y-<12y	>450, or >15% increase from Baseline
	≥12y- <17y	>450, or >15% increase from Baseline
	≥17y	<450, 450-<480, 480-<500, ≥500 or <30, 30-<60, ≥60 increase from Baseline
PR interval (ms)	3y-<12y	>180, or ≥25% increase from Baseline
	≥12y - <17y	>200, or ≥25% increase from Baseline
	≥17y	Treatment-emergent value >200, >220, >250
QRS interval (ms)	3y-<12y	>100, or ≥25% increase from Baseline

	≥12y - <17y	≥110, or ≥25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	3y-<12y	<60, >130
	≥12y	<50, >120

Was revised to:

Table 17 ECGs Abnormality Criteria

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	≥500
	≥12y	≥500 or ≥60 increase from Baseline
QTc(F) (ms)	3y-<12y	>440, or >15% increase from Baseline
	≥12y- <17y	>440, or >15% increase from Baseline
	≥17y	>450, >480[a], ≥500 or ≥60 increase from Baseline
QTc(B) (ms)	3y-<12y	>450, or >15% increase from Baseline
	≥12y- <17y	>450, or >15% increase from Baseline
	≥17y	>450, >480[a], ≥500 or ≥60 increase from Baseline
PR interval (ms)	3y-<12y	>180, or >25% increase from Baseline
	≥12y - <17y	>200, or >25% increase from Baseline
	≥17y	Treatment-emergent value >200, >220, >250
QRS interval (ms)	3y-<12y	>100, or >25% increase from Baseline
	≥12y - <17y	>110, or >25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	3y-<12y	<60, >130
	≥12y	<50, >120

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

Section 11.5, Appendix 5: Tables required for Article 41 (EudraCT), clinicaltrials.gov and Article 46 (European Pediatric Regulation), the following text was changed from:

Disposition and Discontinuation Reasons by Development

Discontinuation due to AEs

Demographics by Development*

Baseline Characteristics by Development*

LCM Overall Exposure by Development*

Study Medication Duration by Development

Incidence of TEAEs by Development – Overview*

Incidence of TEAEs by Development*

Incidence of Serious TEAEs by Development*

Incidence of Non-serious TEAEs*

Incidence of TEAEs by Relationship and Development**

Incidence of TEAEs Leading to Discontinuation by Development*

Incidence of Serious TEAEs by Relationship*

Incidence of Non-serious TEAEs by Relationship*

Incidence of Fatal TEAEs by Relationship*

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

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

Was revised to:

Disposition and Discontinuation Reasons by Development

Discontinuation due to AEs

Demographics by Development

Baseline Characteristics by Development

ILAE Seizure Classification History by Development

Classification of Epileptic Syndrome by Development

AEDs and Benzodiazepines at Study Entry by Development

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

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

Study Medication Duration by Development

Cumulative Study Medication Duration by Development

Study Medication Daily Dosing by Development

Incidence of TEAEs by Development – Overview

Incidence of TEAEs by Development

Incidence of Serious TEAEs by Development

Incidence of Non-serious TEAEs

Incidence of TEAEs by Relationship and Development

Incidence of TEAEs Leading to Discontinuation by Development

Incidence of Serious TEAEs by Relationship

Incidence of Non-serious TEAEs by Relationship

Incidence of Fatal TEAEs by Relationship

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

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

12-Lead ECG Summary by Development

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

Tables in this section are not referred to in the body of the SAP. Tables summarizing Development may show columns for Pediatrics and Adults where Pediatrics are the subjects in EP0012 aged 17 or less and Adults are the subjects in EP0012 aged 18 or more or the table may be generated by Pediatrics and Adults.

Section 11.6, Additional Subgroups to be programmed in ADSL, the following text was added to the end of the section:

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

12.3 Amendment 3

12.3.1 Rationale for the amendment

SAP Amendment 3 was issued because

- Protocol Amendments #4 and #5 occurred,
- CRFs were added to the clinical database (i.e. related to COVID-19, medical history, seizure classification),
- Text was added to address handling COVID-19,
- for seizures, a database change of documenting missing seizure data as “Not Done” for all missing days in the data, in addition to the “Not Done” as reported by the subject; this prompted the changing of the efficacy algorithm for counting PGTCS to no longer assume zero PGTCS for reports of “Not Done”
- new analyses were added involving generalized seizure and all seizure types and

- other analysis items throughout the SAP were also clarified.

12.3.2 Modification and changes

12.3.2.1 Specific changes

The information below was revised from

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018
SAP Amendment #2	10 Oct 2019

Has been revised to:

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018
SAP Amendment #2	10 Oct 2019
SAP Amendment #3	15 Nov 2021

The following list of abbreviations were added:

COVID-19	Coronavirus disease 2019
II	generalized seizures
IIA	absence seizures
IIB	myoclonic seizures
IIE	primary generalized tonic-clonic seizures
IPD	important protocol deviation
MA	markedly abnormal
SAE	serious adverse event
SPD	specification of protocol deviations

Section 1 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol number EP0012.

Has been revised to:

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol number EP0012, through protocol amendment #5; the data summarized will be from EP0012 unless otherwise stated. Since EP0012 is an open-label extension of SP0982, the SP0982 SAP Amendment #4 should be consulted for how variables were calculated for the randomized subjects rolling into EP0012.

Section 2.2.1.1 Primary safety variables,

The primary safety variables are:

- Adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- Incidence of new seizure types during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days during the Treatment Period as compared to the Prospective Baseline Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days during the Treatment Period as compared to the Prospective Baseline Period

Has been revised to:

The primary safety variables are:

- The incidence of TEAEs over the duration of the Treatment Period
- Subject withdrawals due to TEAEs
- Incidence of new appearance of absence of absence and/or myoclonic seizures during the Treatment Period
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days during the Treatment Period as compared to the Prospective Baseline Period
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days during the Treatment Period as compared to the Prospective Baseline Period
- At least 50% worsening in days with absence seizures
- At least 50% worsening in days with myoclonic seizures

Section 2.2.1.2 Secondary safety variables

Secondary safety variables are:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead electrocardiogram (ECG)
- Changes in vital sign measurements (ie, blood pressure (BP) and pulse rate), including body mass index (BMI) and physical (including neurological) examination findings

Has been revised to:

Secondary safety variables are:

- Percentage of treatment-emergent marked abnormalities in hematology and chemistry parameters
- Percent of treatment-emergent marked abnormalities in 12-lead electrocardiogram (ECG)

Percentage of treatment-emergent marked abnormalities in vital sign measurements (ie, blood pressure (BP) and pulse rate)

Section 2.2.1.3 Other safety variables

Other safety variables are:

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

Has been revised to:

Other safety variables are:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-Lead ECGs
- Changes in vital sign measurements (ie. BP and pulse rate), including weight and height and physical (including neurological) examination findings
- Achenbach Child Behavior Checklist (CBCL)1½-5 or CBCL/6-18 (for pediatric subjects only)
- Cognitive function assessment Behavior Rating Inventory of Executive Function (BRIEF)/BRIEF-P (for pediatric subjects only)

Section 2.2.2.3 Other efficacy variables:

The other efficacy variables are:

- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period
- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period
- Percentage of subjects with at least a 50% reduction in PGTCS frequency compared to the Combined Baseline Period
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to the Prospective Baseline Period
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to the Prospective Baseline Period
- Seizure-free status (yes/no) for PGTCS
- Seizure-free status (yes/no) for all generalized seizure types

- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life, and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age for the first two years of treatment
- Change from Baseline in the EQ-5D-3L visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age) for the first two years of treatment
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits for the first two years of treatment
- Number of working or school days lost by subject due to epilepsy for the first two years of treatment
- Number of days with help from a caregiver due to epilepsy for the first two years of treatment

Has been revised to:

The other efficacy variables are:

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

Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age for the first two years of treatment

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

Section 2.2.2.4 Additional efficacy variables was added:

Additional other efficacy variables that will be analyzed in this SAP are:

- Change in days with generalized seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with generalized seizures per 28 days relative to the Prospective Baseline Period
- Change in days with all seizures per 28 days relative to the Prospective Baseline Period
- Percent change in days with all seizures per 28 days relative to the Prospective Baseline Period
- At least a 50% reduction in generalized seizure days compared to the Prospective Baseline Period
- At least a 50% reduction in all seizure days compared to the Prospective Baseline Period
- Seizure-free status (yes/no) for all seizure types
- Duration of PGTCS free intervals
- Duration of all generalized seizure-free intervals
- Duration of all seizure-free intervals

Section 2.3 Study design and conduct:

This is a multicenter, open-label extension study to assess the long-term safety and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTCS in subjects ≥4 years of age with IGE. This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 study as well as eligible Baseline failures from SP0982. 250 subjects from 150 sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, study completers from SP0982 who are eligible for inclusion in EP0012 are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTCS criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTCS during that time or
- Subjects who experience a second PGTCS after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTCS within the 24-week Treatment Period of SP0982

For SP0982 subjects consented under SP0982 Protocol Amendment 5, after the 125th event is confirmed, two classes of subjects will be allowed to enroll in EP0012. Subjects who are being screened will be allowed to directly enroll into EP0012, thus their screening and baseline data will be captured in SP0982 but some of their baseline data may be captured in EP0012. For subjects who are concluding their LCM treatment and tapering in SP0982, these participants will be consented and complete their Safety Follow-Up (thus not receiving any LCM) in EP0012; the data captured in EP0012 will not be transferred to SP0982.

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1.

The study duration and the total number of clinic visits will vary for each subject. For each subject, the study will last from study entry until LCM is approved for use in the subject's country for the treatment of PGTCS in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until the sponsor decides to close the study. It is anticipated that at least 2 years of treatment will be performed to allow for the collection of long-term safety data. If LCM is not approved for use in the subject's country at the time the sponsor closes the study, access to LCM will be provided according to local laws.

The following study periods are defined:

- A Treatment Period lasting at least 2 years.
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator.
  - Subjects tapering off LCM will do so over a period of up to 4 weeks.
  - An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. Following the End of Taper Visit, there will be a 30-day Safety Follow-Up Period. The Safety Follow-Up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-Up telephone contact 30 days after the last dose of study drug.

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

Has been revised to:

This is a multicenter, open-label extension study to assess the long-term safety, tolerability and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTCS (seizure type=IIE) in subjects ≥4 years of age with IGE. This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 study (or have left the primary study at the time of the 125th event, whichever came first) as well as eligible Baseline failures from SP0982. Then, some subjects who tapered in SP0982 after the 125th event may enter EP0012 for the Safety Follow-up only (ICF to be signed beforehand). Up to 250 subjects from 150 to 180 study sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, study completers from SP0982 who are eligible for inclusion in EP0012, SP0982 Safety Follow-up subjects, and Others are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTCS criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTCS during that time or
- Subjects who experience a second PGTCS after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTCS within the 24-week Treatment Period of SP0982
- Subjects who were ongoing in SP0982 when the 125th event occurred

SP0982 Safety Follow-Up subjects

- Subjects tapered in SP0982 after the 125th event occurs will enter EP0012 for the Safety Follow-Up only; these subjects take no study medication in EP0012 and their EP0012 reason for discontinuation is that they are completing SP0982 Follow-up in EP0012.

Other

- Subjects that enrolled in EP0012 that did not fall into the above categories

For SP0982 subjects consented under SP0982 Protocol Amendment 5, after the 125th event is confirmed, two classes of SP0982 subjects will be allowed to enroll in EP0012. Subjects who are being screened in SP0982, at the time of the 125th event, will be allowed to directly enroll into EP0012, thus their screening and baseline data will be captured in SP0982 but some of their baseline data may be captured in EP0012; their treatment information will be captured in EP0012. For subjects who are concluding their SP0982 LCM treatment and tapering, these SP0982 participants will be consented to enroll in EP0012 and complete their Safety Follow-Up

(thus not receiving any LCM) in EP0012; the data captured in EP0012 will not be transferred to SP0982.

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1.

For adult subjects, treatment will continue for at least 2 years. Once 2 years of participation are reached, adult subjects will continue to participate until 1 of the 2 following conditions are met:

- LCM is approved for use for the treatment of PGTCS in subjects with IGE in the subject's country or
- until the latest approval is granted either by EMA, FDA or PMDA.

For pediatric subjects, treatment will continue until 1 of the following 2 conditions are met:

- up to 5 years of participation or
- until the approval of the extension of indication to cover the target age group is granted.

Adult and pediatric subjects are completers if they continue in the study for the maximum duration in their respective region.

The following study periods for the EP0012 protocol (not for the analysis) are defined:

- A Treatment Period lasting at least 2 years for adults enrolled into EP0012 (may be shorter for adults leaving the study when the PGTCS indication approvals are obtained during the course of the study).
- A Treatment Period lasting at least 5 years (238 weeks) for the population less than 18 years old at enrollment in EP0012 (may be shorter as some participants leave the study when the PGTCS indication approvals are obtained during the course of the study).
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator and do not have to perform the tapering (Taper Visit and SFU).
  - Subjects tapering off LCM will do so over a period of up to 4 weeks.
  - An End of Taper Visit (latest 3 days after the final dose) will occur after the final LCM dose for subjects who taper off LCM. Following the End of Taper Visit, there will be a 30-day Safety Follow-Up Period. The Safety Follow-Up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-Up telephone contact 30 days after the last dose of study drug. The same design will apply to some of the subjects tapered in SP0982 at the time of the 125th event and who entered EP0012 for the Safety Follow-Up Visit only and to subjects who entered EP0012 for a Safety Follow-Up Visit after discontinuing SP0982 due to the study stopping.

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

Subjects who entered EP0012 as <18 years and become adults (18 years and older) during the study will remain in the study for at least 5 years (238 weeks).

Section 3.1 General presentation of summaries and analyses, new 2nd paragraph:

All appropriate tables, figures and listings will present the study results by All Subjects, Pediatrics (>=4 to <18 years old in EP0012), and Adults (>=18 years old in EP0012). Study results for assessments given only to pediatric subjects will present information by All Subjects. A pediatric subject is less than 18 years old at EP0012 Visit 1.

Section 3.1 General presentation of summaries and analyses, last 3 paragraphs:

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

Efficacy analyses will be performed on data reported during analysis treatment period. PGTCS analyses will be done on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 days, any PGTCS reported during the gap will not be included in PGTCS summaries.

Safety analyses will be performed on data reported during the analysis treatment period. All data reported in the study will be listed in subject data listings.

Has been revised to:

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

Efficacy analyses will be performed on data reported during the analysis Treatment Period see Section 3.2.1.1) on the Full Analysis Set (FAS). PGTCS analyses will be done on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap >3 consecutive days, any PGTCS reported during the gap will not be included in PGTCS summaries.

Safety analyses (which include analyses on absence (seizure type=IIA) and/or myoclonic seizures (seizure type=IIB)) will be performed on data reported during the analysis Treatment Period for the Safety Set (SS).

Section 3.2.1.1 Analysis periods,

The following analysis periods are defined:

- Treatment Period: The Treatment Period starts at the time of first dose of study medication during the EP0012 study and ends on the date of last dose of study medication or the date of ET Visit or Termination Visit, whichever is later. The Treatment Period includes the protocol-defined Taper Period (see Section 3.2.2) if the subject completes it.
- Post-Treatment Period: The Post-Treatment Period is defined as the treatment free observational phase after the Treatment Period, for the subjects who take LCM in EP0012. It starts on the day after the end date of the Treatment Period and ends on the date of the final

visit or date of last contact with the subject, whichever is later. For the subjects from SP0982 who are completing their Safety Follow-up in EP0012, their entire time in EP0012 will be deemed to be in the Post-Treatment Period due to the subjects not taking LCM in EP0012.

Has been revised to:

The following analysis periods are defined:

- Treatment Period (this analysis Treatment Period differs from the protocol-defined treatment period): The Treatment Period starts at the time of first dose of study medication during the EP0012 study and ends on the date of last dose of study medication or the date of ET Visit or Termination Visit, whichever is later. The Treatment Period includes the protocol-defined Taper Period (see Section 3.2.2) if the subject completes it. In essence, the Treatment Period contains all data between the dates when the subject is being treated with study medication.
  - An efficacy analysis Treatment Period must be calculated for the PGTCS-related analyses. This time period starts at the time of first dose of study medication during the EP0012 study and ends on the date of last dose of study medication.
- Post-Treatment Period: The Post-Treatment Period is defined as the treatment free (ie no study medication) observational phase after the Treatment Period (in SP0982 or EP0012) where study is taken. It starts on the day after the end date of the Treatment Period and ends on the date of the final visit or date of last contact with the subject, whichever is later. For the subjects from SP0982 who are completing their Safety Follow-up in EP0012, their entire time in EP0012 will be deemed to be in the Post-Treatment Period due to the subjects not taking study medication in EP0012.

If the date of last dose of study medication is missing, see imputation rules in Section 4.2.4.

Section 3.2.1.5 Completer cohort:

A completer cohort will be defined as the subset of subjects in the Full Analysis Set (FAS) that were enrolled, treated with LCM for the specified duration of time (allowing gaps of 3 days or less), and have efficacy data available for the duration of the cohort. For example, a 22-week completer cohort consists of subjects from the FAS, treated with LCM for at least 22 weeks and have efficacy data through at least 22 weeks of exposure.

Subjects will be classified as belonging to one or more of the following completer cohorts for the purpose of subgroup analyses:

- 22 weeks
- 46 weeks
- 94 weeks.

Has been revised to:

A completer cohort will be defined as the subset of subjects in the FAS that were enrolled, treated with LCM for the specified duration of time (allowing gaps of 3 days or less), and have efficacy data available for the duration of the treatment exposure stated in the name of the cohort. For example, a 22-week completer cohort consists of subjects from the FAS, treated with LCM for at least 22 weeks and have efficacy data through at least 22 weeks of exposure (Visit 5).

Subjects will be classified as belonging to one or more of the following completer cohorts for the purpose of subgroup analyses:

- 22 weeks
- 46 weeks
- 94 weeks.
- 142 Weeks
- 190 Weeks
- 238 Weeks

Section 3.2.1.5.1 Use of ET or Termination Visit when Scheduled Visits are missing

An adult subject is considered a completer of EP0012 if Visit 11 (Week 94) or ET or Termination visit is completed instead of Visit 11 (and there are no other treatment visits completed) within the window stated below. Visit 11 or Week 94 was chosen as the visit where subjects could complete the study because it was the closest visit occurring to 2 years given the 6 month visit schedule. Subjects also may be deemed completers of EP0012 when they leave the study due to LCM being approved in their region.

If the visit that corresponds to the completer cohort is missing, then ET or Termination visit will be checked to see if this data can be used for the missing visit and to complete the data needed for the completer cohort.

For assessing the 22 and 46 Week completer cohorts, respectively, assess whether the ET visit was completed instead of Visit 5 or Visit 8, respectively; the Termination visit may not be an option for some subjects for the 22 Week or 46 Week Completer cohorts since subjects can only complete the study after 2 years or approval in their region.

Since subjects can complete EP0012 at Week 94 for the 94 Week completer cohort (and for later completer cohorts), if the Week 94 (Visit 11) is missing, then assess whether the Termination or ET visit was completed instead of Visit 11.

The assessment of using Termination or ET visit to determine whether a subject completes a cohort occurs when the subject is missing visit for XX Week Completer Cohort (Week 22 – Visit 5, Week 46 – Visit 8, Week 94 – Visit 11, Week 142 – Visit 13, Week 190 - Visit 15, and Week 238 – Visit 17) and there are no other later protocol-scheduled visits indicating the subject was exposed longer in the study. Review the Protocol's Schedule of Study Assessments to determine the number of weeks (and calculate the expected date) from the prior visit that the Termination or ET visit is expected. The Termination or ET visit must not be any more than 7 days earlier than expected date for XX Week Completer Cohort, as protocol visit windows are ±7 days; if the ET or Termination visit date is too early, the subject did not complete enough exposure to be included in XX Week Completer Cohort.

Subjects in the completer cohort may have their data further presented by smaller time periods within the duration of the completer cohort as presented in Section 3.2.1.6. When a subject qualifies for a particular completer cohort, the subject has data for the entire completer cohort; this means that the subject has data for the smaller time periods within the completer cohort.

Section 3.2.1.6 Time Period

The time periods for the Treatment Period seizure analysis are “0 to 22 Weeks”, “>22 to 46 Weeks”, “>46 to 94 Weeks”, “>94 to 142 Weeks”, “>142 to 190 Weeks”, “>190 to 238 Weeks”, “0 to 46 Weeks”, “0 to 46 Weeks (> 22 Weeks)”, “0 to 94 Weeks”, “0 to 94 Weeks (> 46 Weeks)”, “0 to 142 Weeks”, “0 to 142 Weeks (>94 Weeks)”, “0 to 190 Weeks”, and “0 to 238 Weeks”. Additional time periods will be added based on the visit schedule as subjects progress through the study.

The time periods include all data in the time window of the time period of interest including early termination and end of taper visit data. A calculation may be needed using dates to determine what time period the early termination and end of taper visit data fit into for each subject.

Has been revised to:

Some time period labels are used for completer cohort tables as well as non-completer cohort tables. When the tables present time periods within a completer cohort, the subject, by definition, has data for the entire time period whereas for the non-completer cohort tables, the subject may not have data for the entire time period.

The time periods for the Treatment Period seizure analysis are “0 to 22 Weeks”, “>22 to 46 Weeks”, “>46 to 94 Weeks”, “>94 to 142 Weeks”, “>142 to 190 Weeks”, “>190 to 238 Weeks”, “0 to 46 Weeks”, “0 to 46 Weeks (> 22 Weeks)”, “0 to 94 Weeks”, “0 to 94 Weeks (> 46 Weeks)”, “0 to 142 Weeks”, “0 to 142 Weeks (>94 Weeks)”, “0 to 190 Weeks”, “0 to 238 Weeks” and entire “Treatment Period”. Additional time periods will be added based on the visit schedule as subjects progress through the study. All tables displaying Time Period should show all time periods.

The time periods for the Treatment Period include all data in the time window of the time period of interest including termination, early termination and end of taper visit data. A calculation may be needed using dates to determine what time period the termination, early termination and end of taper visit data fit into for each subject. While completer cohorts and their time periods involve subjects having data for the entire cohort or time period, when it comes to non-completer cohort tables, subjects do not have to have data for the whole Treatment period or time period within the Treatment period.

For example, for non-completer cohort tables, “0 to 46 Weeks” contains all data from all subjects in 0-46 weeks, where Week 46 is Visit 8, if present; if a subject discontinues the study at Visit 4, the subject is still summarized in “0 to 46 Weeks”. “0 to 46 Weeks (>22 Weeks)” contains all data for all subjects who have data through at least Visit 5 (Week 22). If a subject only has data up to Week 14 (Visit 4), the subject will appear in “0 to 46 Weeks” but not in “0 to 46 Weeks (>22 Weeks)”.

Section 3.2.1.7 Visit Algorithm was added:

In determining the date of visits, which is specifically helpful in determining whether patients are members of completer cohorts, the in-clinic date of the visit will be used instead of visit dates from SDTM.SV (the Study Visits SDTM dataset which contain in-clinic and non-clinic visit dates). In-clinic visit dates, firstly from SDTM.VS (Vital Signs), will be used as the date of protocol-specified visits. If a visit is missing in SDTM.VS, then the in-clinic visit date from SDTM.DA (Drug Accountability) will be used as the date of the protocol-specified visit. If a

visit is missing in SDTM.VS and SDTM.DA, then the in-clinic visit date from SDTM.LB (Laboratory Results) will be used as the data of the protocol-specified visit.

Section 3.2.4 AEDs and Benzodiazepines

Antiepileptic drugs (AEDs) and benzodiazepines will be collected on the concomitant and prior medication case report form (CRF) for AEDs. New concomitant AEDs can be added at any time. Stable use of benzodiazepines is allowed as concomitant AEDs. Intermittent use of benzodiazepines is allowed as rescue medication for epilepsy indications with a maximum of 1 dose per week. Benzodiazepines used as rescue medication will be flagged with "RESCUE" in the indication field on the CRF. Rescue AEDs will also be identified programmatically as any AED with an epilepsy or seizure related indication taken intermittently as 1 dose per week.

Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to SP0982 Visit 1.

Was revised to:

Antiepileptic drugs (AEDs) and benzodiazepines will be collected on the concomitant and prior medication case report form (CRF) for AEDs. New concomitant AEDs can be added at any time. Benzodiazepines are AEDs. The UCB study physician will review a listing of all medications and flag which ones are to be summarized as AEDs and benzodiazepines since AEDs may be entered on the wrong medication case report form.

Concomitant AEDs at Study entry, concomitant benzodiazepine use at SP0982 entry, and Lifetime AEDs and Benzodiazepines for subjects randomized in SP0982 are already calculated and carried forward into EP0012. These variables will be summarized.

For EP0012 direct enrollers, concomitant AEDs at study entry are defined as AEDs where the start date is on or before 28 days prior to EP0012 Visit 1 and the medication was still ongoing on the date of Visit 1. Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to EP0012 (direct enrollers) Visit 1; ongoing AEDs are not counted as a lifetime AED. Concomitant benzodiazepine use at EP0012 entry is the use of any benzodiazepine at EP0012 Visit 1.

Stable use of benzodiazepines is allowed as concomitant AEDs. Intermittent use of benzodiazepines is allowed as rescue medication for epilepsy indications with a maximum of 1 dose per week. Benzodiazepines used as rescue medication will be flagged with "RESCUE" in the indication field on the CRF. Rescue AEDs will also be identified programmatically as any AED with an epilepsy or seizure related indication taken for 1 or 2 days, at any frequency.

If a subject is unable to take study medication, commercial lacosamide can be taken instead in order to fill the gaps in exposure. In this instance, the commercial lacosamide usage is considered a substitute for study medication in determining whether a subject has > 3 day LCM gap and counting PGTCS occurring in such a gap; no exposure records will be created to add commercial lacosamide to study medication exposure. The start and end date of commercial LCM usage will be calculated and stored in ADSL for use in PGTCS analyses.

The preferred term reported on the concomitant medication CRF is lacosamide.

Section 3.2.4.1 Phenytoin use was added:

The following preferred terms will be grouped as "Phenytoin": phenytoin, phenytoin sodium, ethotoin, fosphenytoin, fosphenytoin sodium, and zentronal.

Section 3.2.4.2 Valproate use was added:

The following preferred terms will be grouped as "Valproate": valproic acid, valproate semisodium, valproate sodium, valproate magnesium, ergenyl chrono, and valproate.

Section 3.2.4.3 Phenobarbital use was added:

The following preferred terms will be grouped as "Phenobarbital": phenobarbital, phenobarbital sodium, methylphenobarbital, and primidone.

Section 3.3 Definition of Baseline Values

For PGTCS data, the Combined Baseline Period is defined as the combined 12-week Historical and 4-week Prospective Baseline Periods from the SP0982 study. This Period starts 84 days prior to Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study.

For absence and myoclonic seizure data in order to determine Responder Status and worsening, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. In order to determine emergence of new seizure type, the Combined Baseline Period will be used.

For all other data, Baseline values are defined as follows;

- For Baseline failures from SP0982, data collected at Visit 1 prior to the first dose of study medication will be used as Baseline values. Data collected on the date of first dose of study medication will be assumed to be prior to the first dose. For data not collected at Visit 1 prior to the first dose of study medication, the last data collected in SP0982 will be used as Baseline values, if available.

For non-Baseline failures from SP0982, the last non-missing value prior to the first dose of study medication in the SP0982 study will be used as the Baseline value.

Was revised to:

The baseline data for randomized SP0982 subjects in EP0012 will not recalculated. For subjects who directly enrolled into EP0012, some baseline variables may be calculated in SP0982 but these calculations need to be reassessed as detailed below.

For PGTCS data, the Combined Baseline Period is defined as the combined 12-week Historical and 4-week Prospective Baseline Periods from the SP0982 study. The Combined Baseline Period starts 84 days prior to Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. This means that for subjects who directly enrolled into EP0012 (were not randomized in SP0982), the baseline PGTCS (before first dose in EP0012) data from SP0982 is combined with any reported baseline seizure information from EP0012 to recalculate the subject's baseline variables such as PGTCS frequency.

Data from Combined Baseline is used for analyses involving PGTCS since the CRF was specific in asking for PGTCS counts. Other seizure type data recorded in Historical Baseline are deemed less reliable. For seizure calculations involving Absence, Myoclonic, Generalized (seizure type=II) and All seizure types (seizure types = I, II and III), Prospective Baseline data is used;

that means for generalized and all seizure type calculations specifically, PGTCS data in Prospective Baseline will only be used (not the Combined Baseline data) along with the other seizure types.

For absence, myoclonic, generalized and all seizure data, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. This means that for the subjects who directly enrolled into EP0012 (were not randomized in SP0982), the baseline absence, myoclonic, generalized or all (respectively) seizure data from SP0982's Prospective Baseline period is combined with any reported baseline absence, myoclonic, generalized or all (respectively) seizure information from EP0012 (reported before first dose in EP0012) to recalculate the subject's baseline variables such as days with absence, myoclonic, generalized or all seizures per 28 days.

In order to determine emergence of new seizure type, the Combined Baseline Period as well as any seizures reported prior to first dose in EP0012 will be used.

For all other data, Baseline values are defined as follows;

- For Baseline failures from SP0982, data collected at Visit 1 prior to the first dose of study medication will be used as Baseline values. Data collected on the date of first dose of study medication will be assumed to be prior to the first dose. For data not collected at Visit 1 but still prior to the first dose of study medication, the last data collected in SP0982 will be used as Baseline values, if available.
- For non-Baseline failures from SP0982, the last non-missing value prior to the first dose of study medication in the SP0982 study will be used as the Baseline value.

  For quantitative ECG assessments, if repeat measurements pre-first dose, then the average value is used as the Baseline value.

Section 3.4 Protocol Deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

Was revised to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined in the Specification of Protocol Deviation (SPD) document. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without

consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

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

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

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock. A list of subjects with important protocol deviations will be agreed upon during the quarterly IPD meetings and will be documented in the IPD meeting minutes.

In addition, protocol deviations related to the impact of the global pandemic of coronavirus disease 2019 (covid-19) will be documented. Important protocol deviations related to COVID-19 will be included in the important protocol deviations.

Section 3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have a signed Informed Consent/Assent form.

Was revised to:

The Enrolled Set (ES) will consist of all subjects who have a signed Informed Consent/Assent form. Subjects completing SP0982 Safety Follow-up are contained in this analysis population because no study medication is administered to them.

Section 3.5.2 Safety Set

The Safety Set (SS) is a subset of the ES and consists of all subjects who received at least 1 dose of LCM during EP0012.

Was revised to:

The Safety Set (SS) is a subset of the ES and consists of all subjects who received at least 1 dose of LCM during EP0012. All safety analyses will be performed on the SS.

Section 3.5.3 Full Analysis Set

The FAS is a subset of the SS and consists of all subjects with seizure diary data for at least 1 day during EP0012.

Was revised to:

The FAS is a subset of the SS and consists of all subjects with seizure diary data for at least 1 day during EP0012. PGTCS-related analyses will be performed on the FAS.

Section 3.6 Treatment assignment and treatment groups, first sentence:

All subjects will receive LCM.

Has been revised to:

All subjects, except those enrolled to complete Safety-Follow-up in EP0012, will receive LCM.

Section 3.9 Changes to protocol-defined analyses:

There are no changes to analyses specified in the protocol.

Has been revised to:

There are no changes to analyses specified in the protocol however there are additional variables defined in the SAP which are detailed in Section 2.2.2.4 that will be analyzed.

Section 4.2 Handling of dropouts or missing data:

For subjects missing data at the first visit in EP0012, data from SP0982 will be checked as follow:

- for subjects who transitioned from SP0982 to EP0012, final clinic visit data in SP0982 will be checked for data not reported for V1 in EP0012.
- for subjects who are baseline failures or incomplete screen failures in SP0982 who enrolled in EP0012, baseline data will be used from EP0012 V1 (if prior to first EP0012 dose) or the latest data from the screening and baseline visits in SP0982 can be used (also if prior to first EP0012 dose).

Has been revised to:

For subjects missing data at the first visit in EP0012, data from SP0982 will be checked as follow:

- for subjects who transitioned from SP0982 to EP0012, final clinic visit data in SP0982 will be checked for data not reported for V1 in EP0012.
- for subjects who are baseline failures or incomplete screen failures in SP0982 who enrolled in EP0012, baseline data will be used from EP0012 V1 or unscheduled V1 (if prior to first EP0012 dose) or the latest data from the screening and baseline visits in SP0982 can be used (also if prior to first EP0012 dose).

Section 4.2.1 Missing seizure days

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

For the purpose of the derivation of PGTC seizure-free status, in the first 2 years, if there are seizure counts reported as “not done” on a specific day, then the seizure count will be assumed to be zero on that date. For years 3-5, when subjects are only required to enter days when PGTCS occurred, days not reported are assumed to be PGTC seizure-free; if seizure information is known to be missing, then the subject is not PGTC seizure-free.

The calculation of average 28-day PGTCS frequency accounts for missing data in the first 2 years by only evaluating days for which data are available. For years 3-5, the calculation of average 28-day PGTCS frequency uses the seizure information reported since “not done” information is no longer gathered; if there is a known non-compliance in recording seizures and

the unevaluable days can be identified, then the average 28-day PGTCS frequency will use only evaluable days.

For all seizure types, any missing day in the seizure diary during years 1-2 renders a subject to be not seizure-free due to the lack of information.

Absence or myoclonic subjects will be considered for seizure-free evaluation from all generalized seizure types in years 1-2 for the applicable time period if the subject had <10% of days during the time period with seizure data reported as "not done".

For years 3-5, when subjects are only required to enter days when generalized seizures occur, a subject will be considered seizure-free for generalized seizures if the subject has no days reported with generalized seizures (seizure type=II).

Has been revised to:

For evaluations based on seizure diary data, imputation for missing data will not be performed. This means, for example, for an analysis for an interim data cut or for the final analysis, only seizure data for completed visits can be used in the analyses (i.e. study participants should not be assumed to have zero seizures between the time of the last-known visit and the interim cutoff; the subject will appear as having missing seizure information). The calculation of average 28-day seizure frequency or days with seizure per 28 days accounts for missing data by only evaluating days for which the data are available. Additionally for PGTC seizure calculations, PGTCS are not counted during gaps when LCM is not taken > 3 consecutive days.

Section 4.8 Examination of subgroups, the following was added:

- Development (in EP0012) (≥ 4 to <18 years of age, ≥18)

Section 4.10 Use of safety subset of subjects was added:

For absence seizure analyses, the population analyzed will be further restricted to the subset of subjects

- who reported a seizure classification history of absence seizures in either SP0982 or EP0012, or
- who reported absence seizures during Combined Baseline Period, the Treatment Period or Transition Period of SP0982 or
- who reported absence seizures at any time prior to Safety Follow-up in EP0012.

These subjects are hereby referred to as the "Absence subpopulation" because this subgroup only contain subjects who have had or who are having absence seizures.

For myoclonic seizure analyses, the population analyzed will be further restricted to the subset of subjects

- who reported a seizure classification history of myoclonic seizures in either SP0982 or EP0012, or
- who reported myoclonic seizures during Combined Baseline period, the Treatment Period or Transition Period of SP0982 or
- who reported myoclonic seizures at any time prior to Safety Follow-up in EP0012.

These subjects are hereby referred to as the "Myoclonic subpopulation" because this subgroup only contain subjects who have had or who are having myoclonic seizures.

Section 5.1 Subject disposition

The study eligibility criteria and those subjects who did not meet it will be listed for the ES. All disposition data for the ES will be presented in subject data listings.

The number of subjects in the SS and FAS will be presented by investigator; the date of first subject in and date of last subject out will also be included in this summary. The subject populations will be listed.

The overall number and percentage of subjects who completed and discontinued from the study will be presented for the SS and FAS including number and percentages for each reason for discontinuation. The completion of the study is defined as the completion of the Termination Visit. Discontinuation is defined as the completion of the ET Visit. This summary will be repeated for each subgroup as detailed in Section 4.8 for the SS and FAS. The study termination information will be presented in the subject data listings.

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

Has been revised to:

The study eligibility criteria and those subjects who did not meet it will be listed for the ES. All disposition data for the ES will be presented in subject data listings.

The number of subjects in the SS and FAS will be presented by investigator; the date of first subject in and date of last subject out will also be included in this summary. The subject populations will be listed.

The number and percentage of subjects in the ES, SS and FAS will be presented by age at Baseline in SP0982 as well as for all subjects.

The overall number and percentage of subjects who completed and discontinued from the study will be presented for the SS and FAS by age at baseline in SP0982 as well as all subjects including number and percentages for each reason for discontinuation. The completion of the study is defined as the completion of the Termination Visit. Discontinuation is defined as the completion of the ET Visit. The number and percentage of subjects who switch to commercial Vimpat use will be presented. The study termination information will be presented in the subject data listings.

The number and percentages of subjects impacted by COVID-19 will be presented for each visit, overall and by impact category, for all subjects in the SS. These data will be presented in subject data listings.

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

Section 6.1.2 Analysis of demographic variables:

Baseline demographics will be summarized for the SS and include gender, race, ethnicity, age, age category, height (cm), weight (kg) and BMI (kg/m^2). Race and ethnicity will be from the SP0982 study but all other demographic variables will be from EP0012.

Demographics will be listed for all subjects screened.

Has been changed to:

Baseline demographics will be summarized for the SS and include gender, race, ethnicity, age, age category, height (cm), weight (kg) and BMI (kg/m^2); age is calculated in the SDTM as age at enrollment into EP0012 and that variable should be used for defining age category. Race and ethnicity will be from the SP0982 study but all other demographic variables will be from EP0012.

Demographics will be listed for all subjects enrolled.

Section 6.2.2 Analysis of other Baseline characteristics:

The following Baseline characteristics will be presented:

- Time since first diagnosis at date of consent for SP0982
- Age at diagnosis of the disease
- ILAE Seizure classification history from SP0982
- Classification of epileptic syndrome from SP0982
- Lifetime AEDs and Benzodiazepines at SP0982 entry (0, 1-3, 4-6, 7+)
- Baseline PGTCS frequency from SP0982 per 28 days (as continuous data)
- Baseline PGTCS frequency at SP0982 entry (≤2, >2 per 28 days) from Interactive Response Technology (IRT)
- Baseline PGTCS frequency at SP0982 entry (≤2, >2 per 28 days) from CRF
- Concomitant AEDs at SP0982 entry (1, 2, 3).
- Concomitant AEDs at EP0012 entry (0, 1, 2, 3, 4)
- Concomitant benzodiazepine use at SP0982 entry (yes, no)
- Concomitant benzodiazepine use at EP0012 entry (yes, no)
- LCM study drug status (continuing LCM treatment (randomized to LCM in SP0982), new LCM treatment (randomized to PBO or baseline failure from SP0982))
- SP0982 exit status (Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up, SP0982 early discontinuation).

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

Was revised to:

For director enrollers in EP0012, the baseline characteristic variables can represent a combination of baseline data stored in SP0982 as well as EP0012; the subjects continuing from SP0982 are included but their baseline data is from SP0982 only.

Subjects randomized in SP0982 will appear in summaries below denoted as being from “SP0982 entry”. All subjects enrolled in EP0012 will appear in rows that have no reference to SP0982 and the rows denoted as being from “EP0012 entry” or “EP0012”.

The following Baseline characteristics will be presented:

- Time since first diagnosis at date of consent – Time since first diagnosis calculated for all EP0012 subjects; this data is stored in SP0982
- Age at diagnosis of the disease – age at diagnosis calculated for all EP0012 subjects; this data is stored in SP0982ILAE Seizure classification history – see below
- Classification of epileptic syndrome – see below
- Lifetime AEDs and Benzodiazepines (SP0982) (0, 1-3, 4-6, 7+) – categorical representation of lifetime AEDs and Benzos of randomized SP0982 subjects in EP0012; this data is stored in SP0982
- Lifetime AEDs and Benzodiazepines (EP0012) (0, 1-3, 4-6, 7+) – categorical representation of lifetime AEDs and Benzos of all EP0012 subjects
- Combined Baseline PGTCS frequency per 28 days (as continuous data) – baseline PGTCS seizure frequency from CRF of all EP0012 subjects; SP0982 IRT data is not used in EP0012.
- Combined Baseline PGTCS frequency categories (≤2, >2 per 28 days) – baseline PGTCS seizure frequency categorized from CRF of all EP0012 subjects
- Concomitant AEDs at SP0982 entry (0, 1, 2, 3, 4) – categorical representation of concomitant AEDs of randomized SP0982 subjects in EP0012; this data is stored in SP0982
- Concomitant AEDs at EP0012 entry (0, 1, 2, 3, 4) – categorical representation of concomitant AEDs of all EP0012 subjects
- Concomitant benzodiazepine use at SP0982 entry (yes, no, missing) – Yes/No to concomitant Benzo use of randomized SP0982 subjects in EP0012; this data is stored in SP0982
- Concomitant benzodiazepine use at EP0012 entry (yes, no) – Yes/No to concomitant Benzo use of all EP0012 subjects
- LCM study drug status - continuing LCM treatment (randomized to LCM in SP0982), new LCM treatment (randomized to PBO or baseline failure from SP0982 or other)
- SP0982 exit status - Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up, SP0982 early discontinuation.

ILAE Seizure Classification History (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized if it contains the same information as reported in SP0982; EP0012 and SP0982 information will be summarized if additional information is presented in either study. SP0982 information will be summarized if EP0012 contains no updated information.

Classification of Epileptic Syndromes (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized if it contains the same information as reported in SP0982; EP0012 and SP0982 information will be summarized if additional information is presented in either study. SP0982 information will be summarized if EP0012 contains no updated information.

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

Section 6.4 Medical history and concomitant diseases:

Previous and ongoing medical history conditions, initially reported in SP0982 and potentially updated for EP0012, will be summarized by system organ class (SOC) and preferred term (PT) for the SS. A similar summary will be provided for concomitant diseases for the SS. Concomitant diseases are medical history events which are ongoing at the Screening Visit.

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

Was revised to:

Previous and ongoing medical history conditions, initially reported in SP0982 and potentially updated for EP0012, will be summarized by system organ class (SOC) and preferred term (PT) for the subjects in the SS. For medical history events, meaning they are not ongoing, if the same coded condition is reported in both SP0982 and EP0012, only the EP0012 condition will be summarized; if the coded conditions are differently reported in SP0982 and EP0012, then both sets of conditions will be summarized. If no new conditions are reported in EP0012, then only SP0982 conditions will be summarized. A similar summary will be provided for concomitant diseases for the SS. Concomitant diseases are medical history events which are ongoing at the SP0982 Screening Visit or reported as ongoing in EP0012 on the medical history CRF page.

The SP0982 and EP0012 data for the subjects in EP0012, including the SOC, PT and verbatim reported term, will also be presented in data listings. A glossary of medical history SOC and PTs will also be completed.

Section 6.5 Prior and concomitant medications:

Medications with a start date before the first dose of study medication will be considered prior medications. Medications taken on or after the date of the first dose of study medication will be considered concomitant medications. Medications with a missing start date whose stop date is either unknown or after the date of the first dose of study medication will be considered concomitant. Medications with a missing start date whose stop date is prior to the date of the first dose of study medication will be considered as prior medications. Prior AEDs, benzodiazepines and other medications are not summarized for the EP0012 subjects.

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

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

Concomitant AEDs and benzodiazepines taken during the Treatment Period will be summarized by ATC level 4 and PT for the SS.

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

All concomitant medications will be listed. A glossary of ATC codes and associated investigator's terms for all AEDs or benzodiazepines and all other medications (excluding AEDS

and benzodiazepines) will be listed separately in subject data listings. The WHO-DD coding and other information for AEDs or benzodiazepines and all other medications (excluding AEDS and benzodiazepines) will be listed separately in subject data listings.

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

The number of subjects withdrawing to Monotherapy during the Treatment Period will be summarized. Withdrawing to monotherapy means the subject has documentation that all background AEDs [except LCM] were discontinued during Treatment Period) will be summarized. A record for the discontinued AED must be present in the concomitant AED data.

Has been revised to:

Medications with a start date before the first dose of study medication will be considered prior medications. Medications taken on or after the date of the first dose of study medication will be considered concomitant medications. Medications with a missing start date whose stop date is either unknown or after the date of the first dose of study medication will be considered concomitant. Medications with a missing start date whose stop date is prior to the date of the first dose of study medication will be considered as prior medications. Prior AEDs, benzodiazepines and other medications are not summarized for the EP0012 subjects.

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

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

Concomitant AEDs and benzodiazepines taken during the Treatment Period will be summarized by ATC level 4 and PT for the SS.

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

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

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

The number of subjects withdrawing to Monotherapy during the Treatment Period will be identified. Withdrawing to monotherapy means the subject has documentation that all background AEDs [except LCM] were discontinued during Treatment Period. A record for the discontinued background AEDs must be present in the concomitant AED data and study medication must be taken continuously (>3 day gaps are not allowed). For the subjects who withdrew to monotherapy, the following results will be listed:

- Treatment Duration
- Monotherapy Start Date
- Monotherapy End Date

- Duration (days) of monotherapy
- AEDs that were discontinued
- Period when monotherapy starts (0 to Week 46 (V8), >Week 46 to Week 94 (V11), >Week 94 to Week 142 (V13), >Week 142 to Week 190 (V15), >Week 190 (V15)).

The Monotherapy period and the cutoffs are determined for any visit falling within the Treatment Period, after using the definition of Treatment Period from Section 3.2.1.1 and the visit algorithm from Section 3.2.1.7. The start of the Monotherapy period is mapped to the period based on the subject's visit schedule as denoted in the period cutoffs (V8, V11, V13, and V15).

Section 8 Efficacy Analyses:

Analyses of the efficacy variables will be performed using the FAS (unless otherwise stated) and will be descriptive in manner only. Efficacy analyses will be performed on data reported during analysis treatment period. PGTCS analyses will be done on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 days, any PGTCS reported during the gap will not be included in PGTCS summaries.

All seizure diary data will be listed. A listing of subjects excluded from the FAS will also be produced.

Was revised to:

Analyses of the efficacy variables (i.e. PGTCS-related variables) will be performed using the FAS (unless otherwise stated) and will be descriptive in manner only. Efficacy analyses will be performed on data reported during the efficacy analysis Treatment Period. PGTCS analyses will be performed on PGTCS data captured while the subject is taking LCM (gaps 3 days or less are permitted); if a subject experiences an LCM gap > 3 days, any PGTCS reported during the gap will not be included in PGTCS summaries.

Subject seizure information will be imputed with all dates between the start and end of the efficacy Treatment Period; for years 3-5, all days are assumed zero seizure days except those with Not Dones or non-zero counts. Seizure frequency and seizure days will be calculated over non-missing (or evaluable) seizure diary days. Diary days captured as Not Done will not be considered in the calculation of seizure frequency or days with seizure (i.e. unevaluable). Because the evaluation of efficacy is not the primary objective of this study, and because in an uncontrolled study in a variable setting, which allows individualized optimization of study medication and concomitant AEDs, no summaries assessing the impact of missing seizure diary days are planned.

Other seizure variables are considered safety variables and the analysis will be performed using the SS spanning the Treatment Period.

All seizure diary data will be listed. A listing of subjects excluded from the FAS will also be produced.

Section 8.2.1 Derivation of secondary efficacy variable:

The secondary efficacy variable is percent change in PGTCS frequency per 28 days from Combined Baseline Period. In order to account for potential differences in the durations of the study periods for individuals, seizure data will be normalized to 28 days. For years 1-2, seizure

information is collected every day, but for years 3-5 only days with a seizure are recorded. Therefore, from (and including) the day after Visit 11 date to the (and including) date of completion/discontinuation will be assumed to be seizure free days if no seizures are recorded. For years 1-2, only days with a seizure record are considered evaluable

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

SF =

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

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

PCH = [(SFT – SFCB) / SFCB] x 100

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

Was revised to:

The secondary efficacy variable, calculated on the FAS, is percent change in PGTCS frequency per 28 days from Combined Baseline Period for PGTCS data where there is no >3 day LCM gap. In order to account for potential differences in the durations of the study periods for individuals, seizure data will be normalized to 28 days. For years 1-2, (up to and including Visit 11 date), seizure information is collected every day, but for years 3-5 only days with a seizure are recorded. Therefore, from the day after Visit 11 date (inclusive) to the date of the end of the efficacy Treatment Period (inclusive) will be assumed to be seizure free days unless non-zero seizure counts are recorded or the seizure diaries are recorded as being Not Done for those days. For years 1-2, only days with a seizure record other than Not Done are considered evaluable. Also see Section 4.2.1.

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

SF =

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

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

PCH = [(SFT – SFCB) / SFCB] x 100

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

Section 8.2.2 Analysis of secondary efficacy variable:

The percent change in PGTCS frequency during the Treatment Period by Completer Cohort and Time Period will be summarized with descriptive statistics.

The percent change in PGTCS frequency over the Treatment Period by Time Period will be summarized with descriptive statistics.

Was revised to:

The percent change in PGTCS frequency during the efficacy Treatment Period by Completer Cohort and Time Period will be summarized with descriptive statistics. All calculated completer cohorts and time periods will be summarized.

The percent change in PGTCS frequency over the efficacy Treatment Period by Time Period will be summarized with descriptive statistics. All calculated time period results will be summarized.

Section 8.3 Analysis of seizure related other efficacy variables

All seizure data recorded during the Treatment Period will be summarized and listed for the seizure-related other efficacy variables.

For absence seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of absence seizures or reported absence seizures during Baseline or the Treatment Period of SP0982 or EP0012.

For myoclonic seizure analyses, this analysis population will be further restricted to the subset of subjects who reported a history of myoclonic seizures or reported myoclonic seizures during Baseline or the Treatment Period of SP0982 or EP0012.

Was revised to:

All seizure data recorded during the Treatment Period will be summarized and listed for the seizure-related other efficacy variables. Analyses of the other efficacy variables (i.e. absence, myoclonic, generalized and/or all seizure related variables) will be performed using the SS and will be descriptive in manner only. These analyses will be performed on data reported during the Treatment Period.

In section 8.3.1.1 Variable: Days with seizures per 28 days:

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

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

For years 1-2, only days with a seizure record are considered evaluable. However, for years 3-5, from (and including) the day after Visit 11 date to the (and including) date of completion/discontinuation will be assumed to be seizure free days if no seizures are recorded.

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

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

PCH = [(DT – DPB) / DPB] x 100

where DT corresponds to the number of days with absence seizures per 28 days during the relative period and DPB corresponds to the number of days with absence seizures per 28 days during the Prospective Baseline Period from SP0982. If DPB is zero, then PCH will be missing and any such subjects will be excluded from the percent change summary.

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

Have been revised to:

All calculations involving days with seizures per 28 days will be on the SS.

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

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

For years 1-2 (up to and including Visit 11 date), only days with a seizure record other than Not Done are considered evaluable. However, for years 3-5, from the day after Visit 11 date (inclusive) to the date of the end of the efficacy Treatment period (inclusive) will be assumed to be seizure free days if no seizures are recorded or the seizure diaries are not recorded as being Not Done for those days..

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

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

PCH = [(DT – DPB) / DPB] x 100

where DT corresponds to the number of days with absence seizures per 28 days during the relative period and DPB corresponds to the number of days with absence seizures per 28 days during the Prospective Baseline Period. If DPB is zero, then PCH will be missing and any such subjects will be excluded from the percent change summary.

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

Section 8.3.1.2 Variables: Responder status – reduction in PGTCS frequency:

A 50% responder is defined as a subject experiencing ≥50% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest. Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1. A 75% responder is defined as a subject experiencing ≥75% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

Has been revised to:

These variables are calculated on the FAS. A 50% responder is defined as a subject experiencing ≥50% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest. Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1. A 75% responder is defined as a subject experiencing ≥75% reduction in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

Section 8.3.1.3 Variables: Responder status – reduction in days with absence seizures:

A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Response to treatment will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Has been revised to:

These variables are calculated on the Absence subpopulation of the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with absence seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period.

Section 8.3.1.3 Variables: Responder status – reduction in days with myoclonic seizures:

A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982. Response to treatment will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period from SP0982.

Has been revised to:

These variables are calculated on the Myoclonic subpopulation of the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with myoclonic seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with myoclonic seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting myoclonic seizures during the Prospective Baseline Period.

Section 8.3.1.5, Variables: Responder status – reduction in days with generalized seizures is new:

These variables are calculated on the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with generalized (all type II) seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting generalized seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with generalized seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75%

reduction in the number of days with generalized seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting generalized seizures during the Prospective Baseline Period.

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

These variables are calculated on the SS. A 50% responder is defined as a subject experiencing ≥50% reduction in the number of days with all types of seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting any seizures during the Prospective Baseline Period. Response to treatment will be based on the percent change in the number of days with all seizures per 28 days, calculated as described in Section 8.3.1.1. A 75% responder is defined as a subject experiencing ≥75% reduction in the number of days with all seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting any seizures during the Prospective Baseline Period.

Section 8.3.1.5 Variable seizure-free status:

For years 1-2, the following definitions will be used:

For all seizure types, any missing day in the seizure diary during years 1-2 renders a subject to be not seizure-free due to the lack of information.

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary and seizures were assessed (ie, "no seizures" is marked or number is entered as zero). Days in the seizure diary which are marked as "not done" on the CRF will be counted as a seizure-free day from PGTCS.

PGTCS free status will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and reported only a combination of "no PGTC seizures" or "not done" for all days during the time period. If 1 or more PGTCS are reported in the time period or if the seizure data is missing, then the subject does not have PGTCS free status=Yes for the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary and seizures were assessed. An absence or myoclonic subject will be considered for seizure-free evaluation for generalized seizure-free status in years 1-2 for the applicable time period if the subject had <10% of days during the time period with seizure data reported as "not done". If 1 or more seizure type=II seizures are reported in the time period, if there is missing data or if there are 10% or more "Not done" days for an absence and/or myoclonic seizure subject, then the subject does not have generalized seizure-free status=Yes for the time period.

For years 3-5, the following definitions will be used:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary.

Seizure-free status from PGTCS will be determined for a particular time period. A subject will have seizure-free status from PGTCS for the time period if the subject completed the time period and no PGTCS were reported during the time period. If 1 or more PGTCS are reported in the time period, then the subject does not have PGTC seizure-free status=Yes for the time period.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero seizure type=II seizures during the time period. If 1 or more seizure type=II seizures are reported in the time period, then the subject does not have generalized seizure-free status=Yes for the time period.

Has been revised to:

For all seizure types and all subjects, any missing or Not Done day in the seizure diary renders a subject to be not seizure-free on that day due to the lack of information.

Section 8.3.1.7.1 Variable: PGTCS free status is new:

A seizure-free day from PGTCS will be defined as a day where no PGTCS were reported in the seizure diary and seizures were assessed (ie, "no seizures" is marked or number is entered as zero). Days in the seizure diary which are marked as "not done" on the CRF will not be counted as a seizure-free day from PGTCS. A subject with a >3 day LCM gap within the period of interest will not be PGTCS-free for that period.

PGTCS free status will be summarized by completer cohort on the FAS. A subject will have seizure-free status from PGTCS for a completer cohort if the subject are in the completer cohort and reported only "no PGTC seizures" for all days during the completer cohort period. If 1 or more PGTCS are reported in the completer cohort or if the seizure data is Not Done, then the subject has PGTCS free status=No for the completer cohort.

Section 8.3.1.7.2 Variable: Generalized seizure-free status is new:

If missing data is reported, then the subject is not seizure-free from generalized seizures for those missing days.

A seizure-free day from generalized seizures will be defined as a day where no generalized seizures (seizure type=II) were reported in the seizure diary.

A subject will have seizure-free status from all generalized seizure types for the applicable time period if the subject completed the time period and reported zero seizure type=II seizures and no "Not Done" days during the time period for the SS. If 1 or more seizure type=II seizures are reported or if there are "Not Done" seizure diary days in the time period, then the subject has generalized seizure-free status=No for the time period.

Section 8.3.1.8 Variables: all seizure-free status is new:

A seizure-free day from all seizures will be defined as a day where no seizures (seizure type=I, II or III) were reported in the seizure diary.

A subject will have seizure-free status from all seizure types for the applicable time period if the subject completed the time period and reported zero seizures, with no "Not Done" days, during the time period for the SS. If 1 or more seizures are reported or if there are "Not Done" seizure diary days in the time period, then the subject has all seizure-free status=No for the time period.

Section 8.3.1.9 Variable: Worsening of PGTCS:

Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1. Seizure worsening is defined as a subject experiencing ≥50% increase in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

Has been revised to:

Response to treatment will be based on the percent change in PGTCS frequency, calculated as described in Section 8.2.1 on the FAS. PGTCS worsening is defined as a subject experiencing ≥50% increase in PGTCS frequency per 28 days from Combined Baseline Period to the period of interest.

Section 8.3.1.10 Variable: Worsening of days with absence seizures:

Response to treatment will be based on the percent change in days with absence seizures per 28 days, as calculated in Section 8.3.1.1. Worsening is defined as a subject experiencing ≥50% increase in days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

The increase in days with absence seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period from SP0982.

Has been revised to:

Response to treatment will be based on the percent change in days with absence seizures per 28 days on the Absence subpopulation, as calculated in Section 8.3.1.1 on the SS. Worsening is defined as a subject experiencing ≥50% increase in days with absence seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period.

The increase in days with absence seizures per 28 days from Prospective Baseline will be categorized as >0 to 25%, >25 to 50%, >50 to 75%, and >75% to the period of interest, for the subjects reporting absence seizures during the Prospective Baseline Period.

Section 8.3.1.12 Worsening of days with generalized seizures is new:

Response to treatment will be based on the percent change in days with generalized seizures per 28 days, as calculated in Section 8.3.1.1 on the SS. Worsening is defined as a subject experiencing ≥50% increase in days with generalized seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting generalized seizures during the Prospective Baseline Period.

Section 8.3.1.13 Worsening of days with all seizures is new:

Response to treatment will be based on the percent change in days with all seizures per 28 days, as calculated in Section 8.3.1.1 on the SS. Worsening is defined as a subject experiencing ≥50% increase in days with all seizures per 28 days from Prospective Baseline Period to the period of interest, for the subjects reporting all seizures during the Prospective Baseline Period.

Section 8.3.1.14 PGTCS free intervals was added:

PGTCS-free intervals will only be assessed for periods not containing >3 day LCM gap. If the >3 day LCM gap appears in the period of interest, the subject is not PGTCS-free for the interval.

For the FAS, subjects who are PGTCS-free from the date of Visit 1 will be identified as having a PGTCS-free interval from Visit 1. The duration of the PGTCS-free interval will be calculated as date of last day of consecutive PGTCS freedom – date of Visit 1 +1.

To determine the longest interval of PGTCS-freedom, all PGTCS-free intervals will be identified with a calculation of date of last day of PGTCS freedom for Nth interval – date of the first day of PGTCS freedom for the Nth interval + 1. The largest duration of all N intervals will be identified as the longest interval of PGTCS freedom.

To determine the total duration of PGTCS-freedom, all N PGTCS-free intervals will be summed.

Section 8.3.1.15 Generalized seizure free intervals was added:

For the SS, subjects who are generalized seizure-free from the date of Visit 1 will be identified as having a generalized seizure-free interval from Visit 1. The duration of the generalized seizure-free interval will be calculated as date of last day of consecutive generalized seizure freedom – date of Visit 1 +1.

To determine the longest interval of generalized seizure free, all generalized seizure-free intervals will be identified with a calculation of date of last day of consecutive generalized seizure freedom for Nth interval – date of the first day of generalized seizure freedom for the Nth interval + 1. The largest duration of all N intervals will be identified as the longest interval of generalized seizure freedom.

To determine the total duration of generalized seizure freedom, all N generalized seizure-free intervals will be summed.

Section 8.3.1.16 All seizure-free intervals was added:

For the SS, subjects who are all seizure-free from the date of Visit 1 will be identified as having an all seizure-free interval from Visit 1. The duration of the all seizure-free interval will be calculated as date of last day of consecutive all seizure freedom – date of Visit 1 +1.

To determine the longest interval of all seizure free, all seizure-free intervals will be identified with a calculation of date of last day of consecutive all seizure freedom for Nth interval – date of the first day of all seizure freedom for the Nth interval + 1. The largest duration of all N intervals will be identified as the longest interval of all seizure freedom.

To determine the total duration of all seizure freedom, all N all seizure-free intervals will be summed.

Section 8.3.2.1 Analysis: Days with seizures per 28 days:

The following data will be summarized on the SS with descriptive statistics only:

- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort
- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline Age in SP0982 and Time Period
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort

- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Baseline Age in SP0982 and Time Period
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline Age in SP0982 and Time Period
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline age in SP0982 and Completer Cohort.
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Baseline Age in SP0982 and Time Period

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

Was revised to:

The following data will be summarized on the SS by all periods calculated for the Time Period or Completer Cohort with descriptive statistics only:

- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort.
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort.

- Percent change in days with generalized seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort
- Change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period
- Percent change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Completer Cohort.
- Percent change in days with all seizures per 28 days relative to the Prospective Baseline Period by Age at Baseline in SP0982 and Time Period

All seizure days data for absence, myoclonic, generalized and all seizures will be listed. Analyses of the absence seizure related variables will summarize the Absence subpopulation. Analyses of the myoclonic seizure related variables will summarize the Myoclonic subpopulation.

Section 8.3.2.2 Analysis: Responder status – reduction in PGTCS frequency:

The number and percentage of ≥50% and ≥75% responders will be summarized by Time Period and Treatment Period.

Has been revised to:

The number and percentage of ≥50% and ≥75% responders in PGTCS will be summarized on the FAS by Time Period and Treatment Period.

Section 8.3.2.3 Responder status – reduction in days with absence seizures was updated to be on the Absence subpopulation

Section 8.3.2.4 Responder status – reduction in days with myoclonic seizures was updated to be on the Myoclonic subpopulation

Section 8.3.2.5 Responder status – reduction in days with generalized seizures was added:

The number and percentage of ≥50% and ≥75% responders will be summarized on the SS by Time Period and Treatment Period.

Section 8.3.2.6 Responder status – reduction in days with all seizures was added:

The number and percentage of ≥50% and ≥75% responders will be summarized on the SS by Time Period and Treatment Period.

Section 8.3.2.7 Seizure-free status:

The number and percentage of subjects with seizure-free status (yes/no) will be summarized on the SS by Completer Cohort and Treatment Period for the following types of seizures:

- Seizure-free status (yes, no) for PGTCS
- Seizure-free status (yes, no) for all generalized seizure types.

Was revised to:

The number and percentage of subjects with seizure-free status (yes/no) will be summarized by Completer Cohort for the following types of seizures:

- Seizure-free status (yes, no) for PGTCS on the FAS
- Seizure-free status (yes, no) for all generalized seizure types on the SS
- Seizure-free status (yes, no) for all seizure types on the SS.

Section 8.3.2.7.1 PGTCS free intervals was added:

The duration of the following PGTCS-free intervals during the Treatment Period on the FAS will be summarized with descriptive statistics:

- 1st PGTCS free interval from Visit 1
- Longest PGTCS-free interval
- All PGTCS-free intervals

Section 8.3.2.7.2 Generalized seizure-free intervals was added:

The duration of the following generalized seizure-free intervals during the Treatment period will be summarized with descriptive statistics:

- 1st generalized seizure- free interval from Visit 1
- Longest generalized seizure-free interval
- All generalized seizure-free intervals

Section 8.3.2.7.3 All seizure-free intervals was added:

The duration of the following all seizure-free intervals during the Treatment period on the SS will be summarized with descriptive statistics:

- 1st all seizure-free interval from Visit 1
- Longest all seizure-free interval
- All seizure-free intervals

Section 8.3.2.8 Analysis: PGTCS worsening was updated to be on the FAS.

Section 8.3.2.9 Worsening in days with absence seizures was updated to be on the Absence subpopulation

Section 8.3.2.10 Worsening in days with myoclonic seizures was updated to be on the Myoclonic subpopulation

Section 8.4.1.2 PedsQL variables:

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

PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. The PedsQL assessment is retrospective to the prior 4 weeks, and individual items are scored using a 5-point Likert scale (0 to 4 representing responses of: never, almost never, sometimes, often, or

almost always). These scores of 0 to 4 will be transformed by the function: 100 – (response x 25) in order to generate scores of 0, 25, 50, 75, and 100, where a higher value represents a better HRQoL.

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

The above algorithm will also be used to calculate an overall total scale score (all scales) for each subject. To create the Total Scale Score, the mean is computed over the number of items answered on all the Scales

Was revised to:

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations (<18 years), including those with acute or chronic health conditions. Only whole year ages are used. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≤4 years of age. The PedsQL Measurement Model includes developmentally appropriate forms for pediatric subjects>2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. For each subject, the same version that is used at Baseline should be used for 12 months and thereafter the appropriate age versions should be used.

PedsQL generic core scale scores will be calculated for each of the following 4 PedsQL scales: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. For versions intended for subjects >8 years of age, Physical Functioning refers to questions [redacted] Emotional Functioning refers to questions [redacted] Social Functioning refers to questions [redacted] School Functioning refers to questions [redacted]

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

Item transformed score = 100 – (item raw score x 25)

Each PedsQL scale or dimension score is then calculated as the mean of the transformed item scores from items of the considered dimension. In the case of item-level missing data, these will be replaced by the average of non-missing item scores from the considered dimension, if at least 50% of the items from that dimension are non-missing.

The above algorithm will also be used to calculate the PedsQL total score (all items), the psychosocial health summary score (a combination of the emotional, social and school functioning items), and the physical health summary score (the physical functioning items) for each subject. These summary scores will be missing if any of the scale scores contributing to their calculation is missing.

Section 10 Safety analyses was updated with:

Any data that appears in the database (in UCB Findings, Clinical Events, or Findings About) and is not covered by the sections below, will be listed.

Section 10.1.1 Derivation of exposure variables, the following was added:

For pediatric subjects who take both LCM formulations, their tablet dosing in mg/day will be converted to mg/kg/day by dividing the total daily dose in mg/day by the most recently available (relative to the dosing date) body weight in kg. Should a subject receive both oral solution and an oral tablet on the same day, then the individual tablet dose in mg is converted to mg/kg by dividing by the most recently available (relative to the dosing date) body weight, and then the individual dose of oral solution in mg/kg is added to the tablet dose in mg/kg to obtain a total daily dose in mg/kg/day.

Section 10.1.2 Analysis of exposure variables, the following was added:

Pediatric subjects with oral solution (mg/kg/day) and tablet (mg/day) dosing will be summarized two ways: raw (mg/kg/day and mg/day) and converted (mg/kg/day only).

Section 10.2 Adverse events, the following listing was added:

- Subjects experiencing adverse events leading to death on the ES

Section 10.3 Clinical laboratory evaluations, this first paragraph was added:

Clinical laboratory parameters are used in analyses if more than two subjects per visit have a result. All clinical laboratory data appear in listings

Section 10.3 Clinical laboratory evaluations:

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

was revised to:

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

Section 10.4.2.2 Analysis of ECG parameters:

For quantitative ECG measurements (heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT intervals using Bazett and Fridiricia correction methods), summary statistics of the actual values and change from Baseline (where Baseline is from SP0982 as defined in Section 0) will be summarized for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the TEMA ECG criteria age categories. Last visit is the value from the last post-baseline visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values are listed.

Was revised to:

For quantitative ECG measurements (heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT intervals using Bazett and Fridiricia correction methods), summary

statistics of the actual values and change from Baseline (where Baseline is from SP0982 as defined in Section 0) will be summarized for the scheduled visits, overall, Last Visit, minimum and maximum post-Baseline values obtained during the Treatment Period, and in each of the TEMA ECG criteria age categories. Last visit is the value from the last post-baseline visit during the Treatment Period. Repeated or unscheduled ECG assessments during the study will not be presented in by-visit summaries, but will be considered when determining the last visit, minimum, and maximum post-Baseline values during the Treatment Period. If repeat measurements are taken at a particular visit, then the average value is used in summaries and the original values and average value are listed. A subject can be summarized in multiple minimum and maximum post-Baseline categories if the subject appears in multiple age categories (eg, Pediatric subjects) for the continuous data.

Section 10.4.6 Assessment of suicidality:

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

Was changed to:

Subject data listings of the data for the C-SSRS where questions 4 or 5 was answered 'Yes' will be provided. No summaries of the C-SSRS data are planned.

Section 10.4.7.2 Analysis of Achenbach variables:

Calculated T-score values and change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Calculated T-score values and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

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

Was changed to:

Only the syndrome scales presented in Tables 1 and 2 will be analyzed. Raw scores and change from Baseline for each CBCL/1 ½ -5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Raw scores and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

Calculated T-score values and change from Baseline for each CBCL/1½-5 syndrome (aggressive behavior, anxious/depressed, attention problems, emotionally reactive, other problems, sleep problems, somatic complaints, and withdrawn) will be summarized for each visit, and Last Visit.

Calculated T-score values and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

Subject data listings of the data for the Achenbach CBCL will be provided containing the calculated T-scores, raw scores and change from Baseline. The means of the calculated T-score will be plotted by visit.

Section 10.4.8.1 BRIEF-P Scores:

The 2-subscale scores and 5 individual component scores that make up these subscale scores are outlined in Table 3.

Table 3 BRIEF-P questionnaire scoring

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

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

Two validity scales will also be derived: Negativity to assess the extent to which the respondent answers selected BRIEF-P items in an unusually negative manner and Inconsistency to assess the extent to which the respondent answers similar BRIEF-P items in an inconsistent manner. The Negativity scale is the number of items in 30, 44, 46, 47, 53, 55, 56, 57, 59 and 63 with a score of 3, and so has a range of 0 to10. A score of 2 or less is considered acceptable, 3 as elevated and 4 or more highly elevated.

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

Calculated T-score values and change from Baseline for the 2 indexed scores (BRI and MI), and GEC for the BRIEF-P questionnaire will be summarized at each visit, and Last Visit.

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

Was revised to:

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

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

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

Calculated T-score values and change from Baseline for the three index scores (Inhibitory self-control, flexibility and emergent metacognition), the 5 individual component scores and GEC for the BRIEF-P questionnaire will be summarized at each visit, and Last Visit.

All BRIEF-P assessment data will be listed including calculated T-scores, raw scores and changes from Baseline. The means of the BRIEF-P assessment data will be plotted by visit.

Section 10.4.8.2 BRIEF scores, after Table 4:

The BRI score is the total of 28 items and ranges from 28-84. The MI score is the total of 44 items and ranges from 44 to 132.

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

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

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

Calculated T-score values and change from Baseline for the 2 indexed scores (BRI and MI), and GEC for the BRIEF questionnaire will be summarized at each visit, and Last Visit.

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

Was revised to:

The BRI score is the total of 28 items and ranges from 28-84. The MI score is the total of 44 items and ranges from 44 to 132.

T-score values and change from Baseline for the two indexed scores (BRI and MI), the GEC and the 8 individual component scores for the BRIEF questionnaire will be summarized at each visit, and Last Visit.

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

All BRIEF assessment data will be listed including all scales/index scores (raw and T-scores, calculated and change from baseline). The means of the BRIEF assessment data will be plotted.

Section 10.4.9 Safety Seizure Information was updated with:

All analyses will use the relevant data in the SS. The analyses regarding Absence seizure information will be generated on the Absence subpopulation. The analyses regarding the Myoclonic seizure information will be generated on the Myoclonic subpopulation.

Section 11.2.1 List of other significant AEs, the following were added:

Cardiac arrest

Brugada syndrome

Defect conduction intraventricular

Electrocardiogram QT prolonged

Section 11.2.2 List of AEs for PDILI, the following were added:

Alanine aminotransferase increased

Aspartate aminotransferase increased

Section 11.4 Appendix 4: NCI CTC, the following footnote was added:

** Fasting status will be ignored when programming this criteria.

Section 11.5 Appendix 5: Tables required for Article 41, 46 and clinicaltrials.gov:

Disposition and Discontinuation Reasons by Development

Discontinuation due to AEs

Demographics by Development

Baseline Characteristics by Development

ILAE Seizure Classification History by Development

Classification of Epileptic Syndrome by Development

AEDs and Benzodiazepines at Study Entry by Development

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

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

Study Medication Duration by Development

Cumulative Study Medication Duration by Development

Study Medication Daily Dosing by Development

Incidence of TEAEs by Development – Overview

Incidence of TEAEs by Development

Incidence of Serious TEAEs by Development

Incidence of Non-serious TEAEs

Incidence of TEAEs by Relationship and Development

Incidence of TEAEs Leading to Discontinuation by Development

Incidence of Serious TEAEs by Relationship

Incidence of Non-serious TEAEs by Relationship

Incidence of Fatal TEAEs by Relationship

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

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

12-Lead ECG Summary by Development

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

Tables in this section are not referred to in the body of the SAP. Tables summarizing Development may show columns for Pediatrics and Adults where Pediatrics are the subjects in EP0012 aged 17 or less and Adults are the subjects in EP0012 aged 18 or more or the table may be generated by Pediatrics and Adults.

Was revised to Section 11.5 Appendix 5: Tables required for Article 41 (EudraCT):

Discontinuation due to AEs by Development

12.4 Amendment 4

12.4.1 Rationale for the amendment

SAP Amendment 4 was issued because

- Because EP0012 directly enrolled subjects as well as those who rolled over from SP0982, the handling of their data for analysis needed to be clarified and
- A few other analysis items were clarified.

12.4.2 Modification and changes

12.4.2.1 Specific changes

The information below was revised from

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018
SAP Amendment #2	10 Oct 2019
SAP Amendment #3	15 Nov 2021

Has been revised to:

SAP/Amendment Number	Date
Final SAP	20 Dec 2016
SAP Amendment #1	10 Dec 2018
SAP Amendment #2	10 Oct 2019
SAP Amendment #3	15 Nov 2021
SAP Amendment #4	09 Sep 2022

Section 2.3, Study design and conduct, the following:

- Subjects that enrolled in EP0012 that did not fall into the above categories

Was updated to:

- Subjects that enrolled in EP0012 that did not fall into the above categories, like those who were incomplete screeners

The following sentence from the protocol text:

Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1.

Was updated to:

Eligible Baseline failures and incomplete screeners from SP0982 who choose to enter this study will undergo a complete Visit 1.

Section 2.3.1 EP0012 entry status was added:

Subjects who enter EP0012 are either rollovers from SP0982 or direct enrollers in EP0012.

Section 2.3.1.1 Rollover subjects was added:

The subjects enrolled in EP0012 who were randomized in SP0982 and entered EP0012 after discontinuation or completion of SP0982. All study data captured in EP0012 prior to the Safety Follow-up period will be summarized as on-treatment (or during the treatment period) for these subjects, even if the procedure was done before the 1st dose of EP0012 study medication.

Section 2.3.1.2 Direct enrollers was added:

The subjects enrolled in EP0012 who were baseline failures or incomplete screeners in SP0982 who were never randomized to take SP0982 study medication.

Section 2.3.2 Protocol visit windows was added:

Protocol visit windows are ±7 days.

Section 3.2.1.1, Treatment period definition:

The following analysis periods are defined:

- Treatment Period (this analysis Treatment Period differs from the protocol-defined treatment period): The Treatment Period starts at the time of first dose of study medication during the EP0012 study and ends on the date of last dose of study medication or the date of ET Visit or Termination Visit, whichever is later. The Treatment Period includes the protocol-defined Taper Period (see Section 3.2.2) if the subject completes it. In essence, the Treatment Period contains all data between the dates when the subject is being treated with study medication.
  - An efficacy analysis Treatment Period must be calculated for the PGTCS-related analyses. This time period starts at the time of first dose of study medication during the EP0012 study and ends on the date of last dose of study medication.

Was modified to:

The following analysis periods are defined:

- Treatment Period (this analysis Treatment Period differs from the protocol-defined treatment period): The Treatment Period, which will apply to all non-efficacy analyses, starts at the time of first dose of study medication during the EP0012 study for the direct enrollers (date of first visit for rollover subjects) and ends on the date of last dose of study medication or the date of last protocol-defined visit before SFU visit or death date, whichever is later. The Treatment Period includes the protocol-defined Taper Period (see Section 3.2.2) if the subject completes it.
  - An efficacy analysis Treatment Period must be calculated for the PGTCS-related analyses. This time period starts at the time of first dose of study medication during the EP0012 study (date of first visit for rollover subjects) and ends on the date of last dose of study medication or death date, whichever is later.

Section 3.2.1.2 Relative day:

Relative day will be calculated as the current date minus the date of first dose of study medication in EP0012 plus 1 for days on or after the day of first dose of study medication and prior to or on the day of last study medication dose (eg, the day of first dose will be Day 1). Relative day will be calculated as date of first dose of study medication in EP0012 minus the current date for days prior to the first dose of study medication (the day prior to first dose will be Day -1). For days after the last dose of study medication, relative day will be calculated as the

current date minus the date of last dose of study medication including a "+" to denote post treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

Was modified to:

Relative day will be calculated as the current date minus the date of first dose of study medication in EP0012 for direct enrollers (first visit date for rollover subjects) plus 1 for days on or after the day of first dose of study medication and prior to or on the day of last study medication dose (eg, the day of first dose or first visit will be Day 1). Relative day will be calculated as date of first dose of study medication for direct enrollers or first visit for rollovers in EP0012 minus the current date for days prior to the first dose of study medication (the day prior to first dose or first visit will be Day -1). For days after the last dose of study medication, relative day will be calculated as the current date minus the date of last dose of study medication including a "+" to denote post treatment days (eg, the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

Section 3.2.1.5 Completer cohort:

A completer cohort will be defined as the subset of subjects in the FAS that were enrolled, treated with LCM for the specified duration of time (allowing gaps of 3 days or less), and have efficacy data available for the duration of the treatment exposure stated in the name of the cohort. For example, a 22-week completer cohort consists of subjects from the FAS, treated with LCM for at least 22 weeks and have efficacy data through at least 22 weeks of exposure (Visit 5).

Was revised to:

A completer cohort will be defined as the subset of subjects in the FAS that were enrolled, treated with LCM for the specified duration of time (allowing gaps of 3 days or less), and have efficacy data available for the duration of the treatment exposure stated in the name of the cohort minus the visit window (7 days). For example, a 22-week completer cohort consists of subjects from the FAS, treated with LCM for at least 22 weeks minus 7 days and have efficacy data through at least 22 weeks minus 7 days of exposure (Visit 5 or ET visit).

Section 3.2.1.5.1 Use of ET or Termination Visit when Scheduled Visits are missing:

An adult subject is considered a completer of EP0012 if Visit 11 (Week 94) or ET or Termination visit is completed instead of Visit 11 (and there are no other treatment visits completed) within the window stated below. Visit 11 or Week 94 was chosen as the visit where subjects could complete the study because it was the closest visit occurring to 2 years given the 6 month visit schedule. Subjects also may be deemed completers of EP0012 when they leave the study due to LCM being approved in their region.

If the visit that corresponds to the completer cohort is missing, then ET or Termination visit will be checked to see if this data can be used for the missing visit and to complete the data needed for the completer cohort.

For assessing the 22 and 46 Week completer cohorts, respectively, assess whether the ET visit was completed instead of Visit 5 or Visit 8, respectively; the Termination visit may not be an option for some subjects for the 22 Week or 46 Week Completer cohorts since subjects can only complete the study after 2 years or approval in their region.

Since subjects can complete EP0012 at Week 94 for the 94 Week completer cohort (and for later completer cohorts), if the Week 94 (Visit 11) is missing, then assess whether the Termination or ET visit was completed instead of Visit 11.

The assessment of using Termination or ET visit to determine whether a subject completes a cohort occurs when the subject is missing visit for XX Week Completer Cohort (Week 22 – Visit 5, Week 46 – Visit 8, Week 94 – Visit 11, Week 142 – Visit 13, Week 190 - Visit 15, and Week 238 – Visit 17) and there are no other later protocol-scheduled visits indicating the subject was exposed longer in the study. Review the Protocol's Schedule of Study Assessments to determine the number of weeks (and calculate the expected date) from the prior visit that the Termination or ET visit is expected. The Termination or ET visit must not be any more than 7 days earlier than expected date for XX Week Completer Cohort, as protocol visit windows are ±7 days; if the ET or Termination visit date is too early, the subject did not complete enough exposure to be included in XX Week Completer Cohort.

Was revised to:

A subject is considered a completer of EP0012 if Visit 11 (Week 94 = 658 days minus 7 days) or ET or Termination visit is completed instead of Visit 11. Visit 11 or Week 94 was chosen as the visit where subjects could complete the study because it was the closest visit occurring to 2 years given the 6 month visit schedule. Subjects also may be deemed completers of EP0012 when they leave the study due to LCM being approved in their region.

If the visit that corresponds to the completer cohort is missing, then ET or Termination visit will be checked to see if this data can be used for the missing visit and to complete the data needed for the completer cohort.

For assessing the 22 and 46 Week completer cohorts, respectively, assess whether the ET visit was completed instead of Visit 5 (minus 7 days) or Visit 8 (minus 7 days), respectively; the Termination visit may not be an option for some subjects for the 22 Week or 46 Week Completer cohorts since subjects can only complete the study after 2 years or approval in their region.

Since subjects can complete EP0012 at Week 94 (minus 7 days) for the 94 Week completer cohort (and for later completer cohorts), if the Week 94 (Visit 11) is missing, then assess whether the Termination or ET visit was completed instead of Visit 11.

The assessment of using Termination or ET visit to determine whether a subject completes a cohort occurs when the subject is missing visit for XX Week Completer Cohort (Week 22 – Visit 5(minus 7 days), Week 46 – Visit 8 (minus 7 days), Week 94 – Visit 11 (minus 7 days), Week 142 – Visit 13 (minus 7 days), Week 190 - Visit 15 (minus 7 days), and Week 238 – Visit 17 (minus 7 days)) and there are no other later protocol-scheduled visits indicating the subject was exposed longer in the study. Review the Protocol's Schedule of Study Assessments to determine the number of weeks (and calculate the expected date) from the prior visit that the Termination or ET visit is expected. The Termination or ET visit must not be any more than 7 days earlier than expected date for XX Week Completer Cohort, as protocol visit windows are ±7 days; if the ET or Termination visit date is too early, the subject did not complete enough exposure to be included in XX Week Completer Cohort.

Section 3.2.1.6 Time Period, 3rd paragraph:

The time periods for the Treatment Period include all data in the time window of the time period of interest including termination, early termination and end of taper visit data. A calculation will be needed using dates to determine what time period the termination, early termination and end of taper visit data fit into for each subject. While completer cohorts and their time periods involve subjects having data for the entire cohort or time period, when it comes to non-completer cohort tables, subjects may not have data for the whole Treatment period or time period within the Treatment period.

Was revised to:

The time periods for the Treatment Period include all data in the time window of the time period of interest including termination, early termination and end of taper visit data, taking into account the 7 day visit window. A calculation will be needed using dates to determine what time period the termination, early termination and end of taper visit data fit into for each subject, adjusting for the 7 day visit window. While completer cohorts and their time periods involve subjects having data for the entire cohort or time period, when it comes to non-completer cohort tables, subjects may not have data for the whole Treatment period or time period within the Treatment period.

Section 3.2.2 Protocol defined study periods, Taper Period:

up to 4-week period following the Treatment Period for subjects who discontinue from the study at any time. The Taper Period starts the day after the Treatment Period ends and continues until the date of last dose of study medication.

Was revised to:

up to 4-week period following the Treatment Period for subjects who discontinue from the study at any time. The Taper Period starts the day after the Treatment Period ends and continues until the date of last dose of study medication or the End of Taper Visit.

Section 3.2.2 Protocol defined study periods, Safety Follow-up Period:

30-day period following the Taper Period. The Safety Follow-up Period starts the day after the last dose of study medication and continues until the Safety Follow-up telephone contact date.

Was revised to:

30-day period following the Taper Period. The Safety Follow-up Period starts the day after the last dose of study medication or End of Taper Visit and continues until the Safety Follow-up telephone contact date.

Section 3.2.4 AEDs and benzodiazepines:

Concomitant AEDs at Study entry, concomitant benzodiazepine use at SP0982 entry, and Lifetime AEDs and Benzodiazepines for subjects randomized in SP0982 are already calculated and carried forward into EP0012. These variables will be summarized.

For EP0012 direct enrollers, concomitant AEDs at study entry are defined as AEDs where the start date is on or before 28 days prior to EP0012 Visit 1 and the medication was still ongoing on the date of Visit 1. Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to EP0012 (direct enrollers) Visit 1; ongoing AEDs are not counted

as a lifetime AED. Concomitant benzodiazepine use at EP0012 entry is the use of any benzodiazepine at EP0012 Visit 1.

Was revised to:

Concomitant AEDs at SP0982 entry, concomitant benzodiazepine use at SP0982 entry, and Lifetime AEDs and Benzodiazepines for the rollover subjects are already calculated and carried forward into EP0012.

For EP0012 direct enrollers, concomitant AEDs at study entry are defined as AEDs where the start date is on or before 28 days prior to EP0012 Visit 1 and the medication was still ongoing on the date of Visit 1. The concomitant AEDs for the rollover and direct enroller subjects will be presented as Concomitant AEDs at the start of study medication dosing.

Lifetime AEDs are defined as AEDs taken in the subject's history and stopped at least 28 days prior to EP0012 (direct enrollers) Visit 1; ongoing AEDs are not counted as a lifetime AED. The lifetime AEDs for direct enrollers and rollover subjects will be presented as Lifetime AEDs and Benzodiazepines prior to start of study medication dosing

Concomitant benzodiazepine use at EP0012 entry is the use of any benzodiazepine at EP0012 Visit 1. The concomitant benzodiazepine use for direct enrollers and rollover subjects will be presented as Concomitant benzodiazepine use at the start of study medication dosing.

Section 3.3 Baseline values, 1st paragraph:

The baseline data for randomized SP0982 subjects in EP0012 will not recalculated. For subjects who directly enrolled into EP0012, some baseline variables may be calculated in SP0982 but these calculations need to be reassessed as detailed below.

Was revised to:

The baseline data for rollover subjects in EP0012 will not recalculated. For subjects who are direct enrollers, some baseline variables may be calculated in SP0982 but these calculations need to be reassessed as detailed below.

Section 3.3 Baseline values, 4th paragraph:

For absence, myoclonic, generalized and all seizure data, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. This means that for the subjects who directly enrolled into EP0012 (were not randomized in SP0982), the baseline absence, myoclonic, generalized or all (respectively) seizure data from SP0982's Prospective Baseline period is combined with any reported baseline absence, myoclonic, generalized or all (respectively) seizure information from EP0012 (reported before first dose in EP0012) to recalculate the subject's baseline variables such as days with absence, myoclonic, generalized or all seizures per 28 days.

Was revised to:

For absence, myoclonic, generalized and all seizure data, the Prospective Baseline Period is defined as the 4-week Prospective Baseline Period from the SP0982 study. This Period starts the date of Visit 1 of the SP0982 study and ends the day before Visit 2 of the SP0982 study. This means that for the subjects who directly enrolled into EP0012 (were not randomized in SP0982),

the baseline absence, myoclonic, generalized or all (respectively) seizure data from SP0982's Prospective Baseline period is combined with any reported baseline absence, myoclonic, generalized or all (respectively) seizure information in the daily seizure diary from EP0012 (reported before first dose in EP0012) to recalculate the subject's baseline variables such as days with absence, myoclonic, generalized or all seizures per 28 days.

Section 3.3 Baseline values, 6th paragraph:

For all other data, Baseline values are defined as follows;

- For Baseline failures from SP0982, data collected at Visit 1 prior to the first dose of study medication will be used as Baseline values. Data collected on the date of first dose of study medication will be assumed to be prior to the first dose. For data not collected at Visit 1 but still prior to the first dose of study medication, the last data collected in SP0982 will be used as Baseline values, if available.
- For non-Baseline failures from SP0982, the last non-missing value prior to the first dose of study medication in the SP0982 study will be used as the Baseline value.

For quantitative ECG assessments, if repeat measurements pre-first dose, then the average value is used as the Baseline value.

Was revised to:

For all other data, Baseline values are defined as follows;

- For direct enrollers from SP0982, data collected at Visit 1 prior to the first dose of study medication will be used as Baseline values. Data collected on the date of first dose of study medication will be assumed to be prior to the first dose. For data not collected at Visit 1 but still prior to the first dose of study medication, the last data collected in SP0982 will be used as Baseline values, if available.
- For rollover subjects from SP0982, the last non-missing value prior to the first dose of study medication in the SP0982 study will be used as the Baseline value.

For quantitative ECG assessments, if repeat measurements pre-first dose, then the average value is used as the Baseline value.

For direct enrollers, data that is used as the Baseline will be labelled as such. In general, change from baseline for these subjects will be calculated from Visit 2 onward, if the subject has a calculated baseline.

For rollover subjects, change from baseline for these subjects will be calculated from Visit 1 onward, if the subject has a baseline calculation from SP0982.

Section 3.6, paragraphs 2 and 3:

At Visit 1, subjects who completed SP0982 will start on a dose of LCM as follows;

- 10mg/kg/day for pediatric subjects weighing <30kg,
- 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg,
- 400mg/day (200mg twice a day (bid)) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM as follows;

Were revised to:

At Visit 1, rollover subjects will start on a dose of LCM as follows;

- 10mg/kg/day for pediatric subjects weighing <30kg,
- 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg,
- 400mg/day (200mg twice a day (bid)) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Subjects who are direct enrollers into EP0012 will start at Visit 1 on a dose of LCM as follows;

Section 4.2 Handling of dropouts or missing data:

For subjects missing data at the first visit in EP0012, data from SP0982 will be checked as follow:

- for subjects who transitioned from SP0982 to EP0012, final clinic visit data in SP0982 will be checked for data not reported for V1 in EP0012.
- for subjects who are baseline failures or incomplete screen failures in SP0982 who enrolled in EP0012, baseline data will be used from EP0012 V1 or unscheduled V1 (if prior to first EP0012 dose) or the latest data from the screening and baseline visits in SP0982 can be used (also if prior to first EP0012 dose).

Was revised to:

For subjects missing data at the first visit in EP0012, data from SP0982 will be checked as follow:

- for subjects who are rollovers from SP0982 to EP0012, final clinic visit data in SP0982 will be checked for data expected and not reported for V1 in EP0012.
- for subjects who are direct enrollers in EP0012, baseline data will be used from EP0012 V1 or any unscheduled visit (if prior to first EP0012 dose) or the latest data from the screening and baseline visits in SP0982 can be used (also if prior to first EP0012 dose).

Section 4.2.1.1 Week 94 visit – seizure data was added:

At Week 94, subjects switch from using daily seizure diaries (where every date is entered) to using a seizure log (where only non-zero seizures are logged by date). For subjects who continue past Week 94 in the study, if the date of the Week 94 visit is not logged on the daily seizure diary with a non-zero seizure count and it does not appear on the seizure log with a non-zero count, then it can be assumed that 0 seizures occurred on that date.

Section 4.2.3 Incomplete dates for adverse events and concomitant medications, imputation of partial start dates:

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month.

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

Was modified to:

- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollovers is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollovers is the same as the month and year of the start, then use the date of first dose for direct enrollers or first visit for rollover subjects.
- If only the year is specified, and the year of first dose for direct enrollers or first visit for rollover subjects 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 for direct enrollers or first visit for rollover subjects is the same as the year of the start date, then use the date of first dose for direct enrollers or first visit for rollover subjects.
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose for direct enrollers or first visit for rollover subjects, then use the date of first dose for direct enrollers or first visit for rollover subjects.

Section 4.2.3 Incomplete dates for adverse events and concomitant medications, imputation of partial onset dates:

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

Modified to:

- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollover subjects is not the same as the month and year of onset, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose for direct enrollers or first visit for rollover subjects is the same as the month and year of onset, then use the date of first dose for direct enrollers or first visit for rollover subjects
- If only the year is specified, and the year of first dose for direct enrollers or first visit for rollover subjects 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 for direct enrollers or first visit for rollover subjects is the same as the year of onset, then use the date of first dose direct enrollers or first visit for rollover subjects
- If the AE onset date is completely unknown, then use the date of first dose for direct enrollers or first visit for rollover subjects

Section 5.1 Subject disposition, new 5th paragraph was added:

To assess what happens with subjects during the first 94 weeks of the study, the number and percentage of subjects who completed this time period, completed the study before 94 weeks and discontinued during this time period will be presented for the SS and FAS by age at baseline in SP0982 as well as all subjects including number and percentages for each reason for discontinuation during this time period.

Section 6.2.2 Analysis of other Baseline characteristics, paragraph 3:

The following Baseline characteristics will be presented:

- Time since first diagnosis at date of consent – Time since first diagnosis calculated for all EP0012 subjects; this data is stored in SP0982
- Age at diagnosis of the disease – age at diagnosis calculated for all EP0012 subjects; this data is stored in SP0982ILAE Seizure classification history – see below
- Classification of epileptic syndrome – see below
- Lifetime AEDs and Benzodiazepines (SP0982) (0, 1-3, 4-6, 7+) – categorical representation of lifetime AEDs and Benzos of randomized SP0982 subjects in EP0012; this data is stored in SP0982
- Lifetime AEDs and Benzodiazepines (EP0012) (0, 1-3, 4-6, 7+) – categorical representation of lifetime AEDs and Benzos of all EP0012 subjects
- Combined Baseline PGTCS frequency per 28 days (as continuous data) – baseline PGTCS seizure frequency from CRF of all EP0012 subjects; SP0982 IRT data is not used in EP0012.
- Combined Baseline PGTCS frequency categories (≤2, >2 per 28 days) – baseline PGTCS seizure frequency categorized from CRF of all EP0012 subjects
- Concomitant AEDs at SP0982 entry (0, 1, 2, 3, 4) – categorical representation of concomitant AEDs of randomized SP0982 subjects in EP0012; this data is stored in SP0982

- Concomitant AEDs at EP0012 entry (0, 1, 2, 3, 4) – categorical representation of concomitant AEDs of all EP0012 subjects
- Concomitant benzodiazepine use at SP0982 entry (yes, no, missing) – Yes/No to concomitant Benzo use of randomized SP0982 subjects in EP0012; this data is stored in SP0982
- Concomitant benzodiazepine use at EP0012 entry (yes, no) – Yes/No to concomitant Benzo use of all EP0012 subjects
- LCM study drug status - continuing LCM treatment (randomized to LCM in SP0982), new LCM treatment (randomized to PBO or baseline failure from SP0982 or other)
- SP0982 exit status - Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up, SP0982 early discontinuation.

ILAE Seizure Classification History (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized if it contains the same information as reported in SP0982; EP0012 and SP0982 information will be summarized if additional information is presented in either study. SP0982 information will be summarized if EP0012 contains no updated information.

Classification of Epileptic Syndromes (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized if it contains the same information as reported in SP0982; EP0012 and SP0982 information will be summarized if additional information is presented in either study. SP0982 information will be summarized if EP0012 contains no updated information.

Was revised to:

The following Baseline characteristics will be presented:

- Time since first diagnosis at date of consent – Time since first diagnosis calculated for all EP0012 subjects; this data is stored in SP0982
- Age at diagnosis of the disease – age at diagnosis calculated for all EP0012 subjects; this data is stored in SP0982ILAE Seizure classification history – see below
- Classification of epileptic syndrome – see below
- Lifetime AEDs and Benzodiazepines (EP0012) (0, 1-3, 4-6, 7+) – categorical representation of lifetime AEDs and Benzos of all EP0012 subjects
- Combined Baseline PGTCS frequency per 28 days (as continuous data) – baseline PGTCS seizure frequency from CRF of all EP0012 subjects; SP0982 IRT data is not used in EP0012.
- Combined Baseline PGTCS frequency categories (≤2, >2 per 28 days) – baseline PGTCS seizure frequency categorized from CRF of all EP0012 subjects
- Concomitant AEDs at EP0012 entry (0, 1, 2, 3, 4) – categorical representation of concomitant AEDs of all EP0012 subjects
- Concomitant benzodiazepine use at EP0012 entry (yes, no) – Yes/No to concomitant Benzo use of all EP0012 subjects

- LCM study drug status - continuing LCM treatment (randomized to LCM in SP0982), new LCM treatment (randomized to PBO or baseline failure from SP0982 or other)
- SP0982 exit status - Baseline failure, 24-week completer, met exit criteria, incomplete screener, SP0982 safety follow-up, SP0982 early discontinuation
- EP0012 entry status – Direct enroller, rollover.

ILAE Seizure Classification History (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized if it contains the same information as reported in SP0982; EP0012 and SP0982 information will be summarized if additional information is presented in either study. SP0982 information will be summarized if EP0012 contains no updated information.

Classification of Epileptic Syndromes (SP0982 + EP0012): On a subject level, information reported in EP0012 will be summarized. SP0982 information will be summarized if EP0012 contains no updated information.

Section 6.3 Subgroups:

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

Was revised to:

All subgroups detailed in Section 4.8 will be summarized in a table for the SS and FAS. Other subgroups that will be summarized using SP0982 baseline information are:

- Baseline age in SP0982 (4 to <12 years, 12 to < 18 years, 18 to < 65 years, ≥65 years)
- Age for PedsQL (4 years, 5 to 7 years, 8 to 12 years, 13 to <18 years)
- Age for Achenbach CBCL (4 to 5 years, 6 to 18 years)
- Age for BRIEF-P/BRIEF (4 years, 5 to 18 years).

Section 6.5 Prior and concomitant medications, 1st paragraph:

Medications with a start date before the first dose of study medication will be considered prior medications. Medications taken on or after the date of the first dose of study medication will be considered concomitant medications.

Was revised to:

Medications with a start date before the first dose of study medication for direct enrollers will be considered prior medications. Medications taken on or after the date of the first dose of study medication will be considered concomitant medications; medications taken by rollover subjects which are ongoing and concomitant in SP0982 will be considered concomitant in EP0012.

Section 6.5, Prior and concomitant medications, 8th paragraph:

The number of subjects withdrawing to Monotherapy during the Treatment Period will be identified. Withdrawing to monotherapy means the subject has documentation that all background AEDs [except LCM] were discontinued during Treatment Period. A record for the discontinued background AEDs must be present in the concomitant AED data and study

medication must be taken continuously (>3 day gaps are not allowed). For the subjects who withdrew to monotherapy, the following results will be listed:

- Treatment Duration
- Monotherapy Start Date
- Monotherapy End Date
- Duration (days) of monotherapy
- AEDs that were discontinued

Was revised to:

The number of subjects entering EP0012 on or withdrawing to Monotherapy during the Treatment Period will be identified. Entering EP0012 on Monotherapy means the subject has no documented AEDs that are ongoing at first dose. Withdrawing to monotherapy means the subject has documentation that all background AEDs [except LCM] were discontinued during Treatment Period. A record for the discontinued background AEDs must be present in the concomitant AED data and study medication must be taken continuously (>3 day gaps are not allowed). For the subjects who withdrew to monotherapy, the following results will be listed:

- Exposure
- Monotherapy Start Date
- Monotherapy End Date
- Duration (days) of monotherapy
- Concomitant AEDs that were discontinued

Section 8.4.2.2 PedsQL variables:

The observed values and change from Baseline for the total scale score and each of the 4 scale scores will be summarized for each visit and Last Visit. Subgroup summaries by age will be performed using the age groupings for which different questionnaires were entered: 4 years, ≥5 to ≤7 years, ≥8 to ≤12 years, and ≥13 to ≤18 years.

Was revised to:

The observed values and change from Baseline for the total scale score and each of the 4 scale scores will be summarized for each visit and Last Visit. If a subject has a baseline calculated for the 2-4 year old PedsQL, due to the difference in questionnaires, this baseline should not be used for calculating change from baseline for the older aged questionnaires. For the 5-7 year old, 8-12 year old and 13-18 year old questionnaires, if the baseline was calculated from an younger aged questionnaire (except the 2-4 year old questionnaire) as the subject ages from 8 through 18 years old, change from baseline can use the younger aged baseline.

Section 10.1.1 Derivation of exposure variables

Study medication treatment duration (days) will be calculated as follows:

(last study medication dose – first study medication dose) + 1 day.

Gaps in treatment or days with unknown dosing will not be subtracted from the duration of exposure.

Subject-years of exposure is the total treatment duration in days divided by 365.25.

Was modified to:

Study medication treatment duration (days) will be calculated as follows for direct enrollers:

(last study medication dose – first study medication dose) + 1 day.

Study medication treatment duration (days) will be calculated as follows for rollover subjects:

(last study medication dose – visit 1 date) + 1 day.

Gaps in treatment or days with unknown dosing will not be subtracted from the duration of exposure.

Subject-years of exposure is the total study medication treatment duration in days divided by 365.25.

Section 10.1.1 Derivation of exposure variable, 7th paragraph:

For pediatric subjects who take both LCM formulations, their tablet dosing in mg/day will be converted to mg/kg/day by dividing the total daily dose in mg/day by the most recently available (relative to the dosing date) body weight in kg. Should a subject receive both oral solution and an oral tablet on the same day, then the individual tablet dose in mg is converted to mg/kg by dividing by the most recently available (relative to the dosing date) body weight, and then the individual dose of oral solution in mg/kg is added to the tablet dose in mg/kg to obtain a total daily dose in mg/kg/day.

Was revised to:

Because some pediatric subjects take both LCM formulations, dosing will be presented for all subjects within the formulation taken; this will be presented as raw dosing and some pediatric subjects will be summarized in both formulations. For pediatric subjects who take both LCM formulations, their tablet dosing in mg/day will be converted to mg/kg/day by dividing the total daily dose in mg/day by the most recently available (relative to the dosing date) body weight in kg; this will be presented as converted dosing and the summaries of subject data by formulation will be mutually exclusive. Should a subject receive both oral solution and an oral tablet on the same day, then the individual tablet dose in mg is converted to mg/kg by dividing by the most recently available (relative to the dosing date) body weight, and then the individual dose of oral solution in mg/kg is added to the tablet dose in mg/kg to obtain a total daily dose in mg/kg/day.

Section 10.2 Adverse events, 2nd paragraph:

Adverse events will be considered treatment-emergent if the event had onset on or after the date of the first study medication dose in EP0012 and within 30 days following the last study medication dose or events whose intensity worsened on or after the date of first study medication dose and within 30 days following the date of last study medication administration.

Was revised to:

Adverse events will be considered treatment-emergent if the event had onset on or after the date of the first study medication dose in EP0012 and within 30 days following the last study

medication dose or events whose intensity worsened on or after the date of first study medication dose and within 30 days following the date of last study medication administration. Adverse events which were ongoing and treatment-emergent in SP0982 will remain treatment-emergent in EP0012 for rollover subjects.

Section 10.2 Adverse events, 8th paragraph:

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

Was revised to:

The dose at onset TEAE summaries will be presented by the LCM dosing categories presented in Section 10.1.2. Adverse events of unknown dosing are those with no known dose or known dosing and partial AE start or stop dates. TEAEs which were ongoing from SP0982 will be presented for the dose the subject was taking on the date of first dose in EP0012.

Section 10.3 Clinical laboratory evaluations, 5th paragraph:

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

Was revised to:

A table summarizing the number of subjects meeting the potential drug induced liver injury (PDILI) criteria during the Treatment Period will also be presented. The categories for PDILI that will be presented are:

- ≥3xULN in ALT Or AST and ≥2xULN total bilirubin and ≥2xULN of alkaline phosphatase
- ≥3xULN in ALT Or AST and ≥2xULN total bilirubin
- ≥5xULN in ALT or AST
- ≥8xULN in ALT or AST
- ≥3xULN in ALT or AST and the presence of symptoms
- ≥3-<5xULN and baseline ≥2xULN in ALT or AST and <2xULN total bilirubin and no presence of symptoms
- ≥5xULN and baseline ≥2xULN in ALT Or AST and <2xULN total bilirubin.

Section 10.4.1 Vital signs, 2nd paragraph:

The number and percentage of subjects with at least 1 TEMA value will be presented at each post-Baseline visit, Last Visit, Early Termination Visit and minimum and maximum post-Baseline values obtained during the Treatment Period. Percentages will be relative to the number of subjects with a value at each time point.

Was revised to:

Treatment emergent abnormalities of vital signs, the criteria that do not involve a comparison to baseline, are those that were observed during the Treatment Period at scheduled visits and not reporting the abnormality during the Baseline Period. The number and percentage of subjects

with at least 1 TEMA value will be presented at each post-Baseline visit, Last Visit, Early Termination Visit and minimum and maximum post-Baseline values obtained during the Treatment Period. Percentages will be relative to the number of subjects with a value at each time point.

Section 10.4.6 Assessment of suicidality, 2nd paragraph:

Subject data listings of the data for the C-SSRS where questions 4 or 5 was answered 'Yes' will be provided. No summaries of the C-SSRS data are planned.

Was revised to:

Subject data listings of the data for the C-SSRS where questions 4 or 5 was answered 'Yes' will be provided since this is a study withdrawal criteria. No summaries of the C-SSRS data are planned.

Section 10.4.7.2 Analysis of Achenbach variables, 2nd paragraph:

Raw scores and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit.

Was revised to:

Raw scores and change from Baseline for each CBCL/6-18 syndrome (aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed) will be summarized for each visit, and Last Visit. If a subject has a baseline calculated for the CBCL/1 ½ -5 syndrome, that baseline should not be used for calculating change from baseline for the CBCL/6-18 syndrome.

Section 10.4.8.2 BRIEF scores, 5th paragraph:

T-score values and change from Baseline for the two indexed scores (BRI and MI), the GEC and the 8 individual component scores for the BRIEF questionnaire will be summarized at each visit, and Last Visit.

Was revised to:

T-score values and change from Baseline for the two indexed scores (BRI and MI), the GEC and the 8 individual component scores for the BRIEF questionnaire will be summarized at each visit, and Last Visit. If a subject has a baseline calculated for the BRIEF-P, that baseline should not be used for calculating change from baseline for the BRIEF.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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