STATISTICAL ANALYSIS PLAN

Study: EP0100

Product: Levetiracetam

AN OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY OF LEVETIRACETAM AS MONOTHERAPY OR ADJUNCTIVE TREATMENT OF PARTIAL SEIZURES IN PEDIATRIC EPILEPTIC SUBJECTS RANGING FROM 1 MONTH TO LESS THAN 4 YEARS OF AGE

SAP/Amendment Number	Date
SAP/Amendment 1	04 Jun 2019
SAP/Amendment 2	18 Jun 2021
SAP/Amendment 3	03 May 2022

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LIST OF ABBREVIATIONS

ADF	Average Daily Frequency
AE	Adverse Event
AED	Anti-Epileptic Drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
CfB	Change from Baseline
CI	Confidence Interval
BLOCF	Baseline Observation Carry Forward
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DEM	Data Evaluation Meeting
DRC	Daily Record Card
eCRF	electronic Case Report Form
ECG	electrocardiogram
EDV	Early Discontinuation Visit
EEG	electroencephalogram
FAS	Full Analysis Set
FAS_A	Full Analysis Set (Adjunctive therapy)
FAS_M	Full Analysis Set (Monotherapy)
ILAE	International League Against Epilepsy
IPD	Important Protocol Deviations
LEV	Levetiracetam
LLOQ	Lower Limit Of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
M&S	Modeling and Simulation
NDA	New Drug Application
PCS	Possibly Clinically Significant
PCST	Possibly Clinically Significant Treatment-emergent

PD	Pharmacodynamic
PDILI	Potential Drug-Induced Liver Injury
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PK-PPS_A	Pharmacokinetic Per Protocol Set (Adjunctive therapy)
PK-PPS_M	Pharmacokinetic Per Protocol Set (Monotherapy)
PPS	Per Protocol Set
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
SS_A	Safety Set (Adjunctive therapy)
SS_M	Safety Set (Monotherapy)
TEAE	Treatment-Emergent Adverse Event
VNS	Vagal Nerve Stimulation

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the clinical study report for EP0100. Unless specified below, the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP may be amended accordingly. If needed, revisions to the approved SAP may be made prior to the snapshot of the database needed for NDA submission. For regulatory purposes, two planned data cut-offs will be made when the final subject who completes the Evaluation Period reaches Visit 13 and Visit 16 in order to obtain 6-month and 12-month exposure data, respectively.

In addition to above, an interim analysis (IA) was performed for providing PMDA with the latest information to discuss if the study can be discontinued and the application method can be changed to extrapolation strategy based on the results of the IA, which is based on the suggestion at the consultation meeting with PMDA held on [redacted]. The IA was performed according to the eCRF snapshot on 04 Jun 2021, in which the data cut-off date was 30 Apr 2021.

2 PROTOCOL SUMMARY

This is an open-label, single arm study which aims to study Levetiracetam as monotherapy or adjunctive treatment of partial seizures in pediatric epileptic subjects ranging from 1 month to less than 4 years of age. This SAP is based upon the final Protocol EP0100 Amendment 3:

Protocol Date: 06 Feb 2017

Amendment 1: 16 Jun 2017
Amendment 2: 28 Jun 2018
Amendment 3: 29 Jan 2020

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to confirm the efficacy of Levetiracetam (LEV) in reducing seizure frequency in the First Period compared to historical control as adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures.

2.1.2 Secondary Objectives

The secondary objectives are the following:

- To evaluate the safety and tolerability of LEV in the First Period in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate the efficacy of LEV in reducing seizure frequency in the First Period compared to historical control as monotherapy in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

- To evaluate long-term safety and tolerability of LEV in the combined First and Second Periods in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures receiving long-term treatment with LEV at individualized doses
- To evaluate the efficacy of LEV in the combined First and Second Periods as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To characterize pharmacokinetics (PK) of LEV in the First and Second Periods in epileptic pediatric subjects aged 1 month to <4 years

2.2 Study Variables

2.2.1 Efficacy Variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

2.2.1.1 Efficacy Variables for Subjects on Adjunctive Therapy

2.2.1.1.1 Primary Efficacy Variable

First Period:
The primary efficacy variable for subjects on adjunctive therapy is the percent reduction in partial seizure frequency per week from Baseline to Visit 6.
Combined First and Second Periods:
There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

2.2.1.1.2 Secondary Efficacy Variables

First Period:

The secondary efficacy variable for the First Period is the following:

- Percent reduction in partial seizure frequency per week from Baseline to Visit 4 and Visit 5

Note: here and further on, percent reduction is percent reduction from Baseline. Visit, without analysis, refers to study visit.

Combined First and Second Periods:

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline
- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

For definition of analysis visit see Table 3–2.

2.2.1.1.3 Other Efficacy Variables

First Period

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded prior to Protocol Amendment 3 are the following:

- Percent reduction in average daily frequency (ADF) of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

Note: percent reduction is percent reduction from Baseline.

Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all type of seizure frequency per week from Baseline
- For each visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

2.2.1.2 Efficacy Variables for Subjects on Monotherapy

2.2.1.2.1 Primary Efficacy Variable

There is no primary efficacy variable for subjects on monotherapy.

2.2.1.2.2 Secondary Efficacy Variables

First Period:

There is no secondary efficacy variable for the First Period.

Combined First and Second Periods:

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

Note: for definition of analysis visit see Table 3–2.

2.2.1.2.3 Other Efficacy Variables

First Period:

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded prior to Protocol Amendment 3 are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

Note: percent reduction is percent reduction from Baseline.

Combined First and Second Periods:

The other efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in all types of seizure frequency per week from Baseline
- For each analysis visit, percent reduction in all types of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%
- Percentage of subjects who are continuously 6-month seizure-free monitored by the patient diary

2.2.2 Pharmacokinetic/Pharmacodynamic Variable(s)

Levetiracetam (parent compound only) plasma level is defined as the other PK variable.

2.2.3 Safety Variables

2.2.3.1 Primary Safety Variable

There is no primary safety variable.

2.2.3.2 Secondary Safety Variables

The secondary safety variables for the First Period are the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of serious adverse events (SAEs)
- Incidence of TEAEs leading to discontinuation from study medication

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs leading to discontinuation from study medication

2.2.3.3 Other Safety Variables

The other safety variables are the following:

- Adverse events (variables other than secondary safety variables)
- Laboratory tests (blood chemistry and hematology)
- Vital signs
- Body weight and height
- Physical and neurological examination

Additional details are mentioned in the safety analyses section.

2.3 Study Design and Conduct

EP0100 is a Phase 3, open-label, single-arm, multicenter study with LEV as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV (14mg/kg/day to 42mg/kg/day for subjects aged at 1 month to <6 months, 20mg/kg/day to 60mg/kg/day for subjects aged at 6 months to <4 years) in the treatment of partial seizures over the First Period (6 weeks), followed by the long-term follow-up (Second Period) in pediatric subjects.

First Period

Eligible subjects will enter the First Period (6 weeks). For dosing scheme refer to the protocol, Section 5.1.2.

At Visit 6 (Week 6), subjects may enter either the Second Period or the Down-Titration Period, followed by the Safety Follow-Up Period. Subjects who do not enter the Second Period will be down-titrated.

Second Period

Subjects who complete the First Period will have a visit every 4 weeks ±7 days relative to the Visit 3 for the first 6 months of administration and then every 12 weeks ±14 days thereafter.

A final visit will be required approximately 2 weeks ±7 days after the final dose of LEV, or sooner if the subject will continue LEV (prescribed by the primary care provider as commercial LEV) after study completion.

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

The planned number of subjects to be enrolled in the First Period will be a total of 38 subjects for the primary efficacy analysis. Subjects will be enrolled into 4 age groups (1 month to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <4 years), with a minimum of 5 subjects in each age group.
The planned number of monotherapy subjects will be a total of 10 subjects.

It is planned to have those subjects recruited in approximately 20 sites.

2.3.1 Study Periods

- **Retrospective Baseline Period**
  Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline Period.
- **First Period**
  - Selection Period (maximum of 9 days)
  - Evaluation Period (6 weeks)
  - Down-Titration Period (up to 4 weeks)
  - Safety Follow-Up Period (2 weeks)
- **Second Period**

- Maintenance Period (until approval or the program is discontinued)
- Down-Titration Period (up to 4 weeks)
- Safety Follow-Up Period (2 weeks)

2.3.2 Adjunctive Therapy and Monotherapy

Subject who took at least 1 AED at Visit 1 will be categorized as a subject on adjunctive therapy, otherwise the subject will be categorized as on monotherapy (See Section 6.8 for identification of AEDs).

2.4 Determination of Sample Size

Based on the previous placebo-controlled clinical studies for pediatric epilepsy patients that evaluated AEDs, the percent reduction in ADF of partial seizure frequency from Baseline for placebo is assumed to be no more than 10%. For the purposes of this study, a percent reduction in ADF of partial seizure frequency ≤10% is defined as non-effective. Therefore, when the lower limit of 95% confidence interval (CI) of median in the percent reduction in ADF of partial seizure frequency for LEV is greater than 10%, statistical significance is declared. Based on the N01009 data for the percent reduction in ADF of partial seizure frequency for LEV, a population of size N was randomly sampled with replacement repeatedly for 10,000 times for the sample size consideration. The probability was evaluated that the lower limit of 95% Confidence Interval (CI) of median in the percent reduction in ADF of partial seizure frequency for LEV was greater than 10% by samples with size of N. A sample size of at least 34 subjects is required to obtain 90% power. Assuming 10% of subjects will be non-evaluable, 38 subjects will be enrolled.

Due to the change in the primary efficacy variable in protocol amendment 3, the sample size was reconsidered. When the placebo rate area is conservatively redefined as ≤15% and assuming there are no nonevaluable subjects, a sample size of 38 subjects will obtain ≥80% power. Therefore, no change in sample size is required.

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 for the non-PK analysis will be performed using SAS Version 9.3 or higher.

The study will enroll subjects from different age when entered into the study, see Section 4.8.

The following subgroups are formed: 1 month to <6 months, 6 months to <1 year, 1 year to <2 years and 2 years to <4 years. It is anticipated that a small number of subjects will be enrolled into the 1 month to <6 months and the 6 months to <1 year age categories. Hence, for analysis of the primary efficacy variable the data of the two youngest age categories will be pooled into one category resulting in three age categories: 1 month to <1 year, 1 year to <2 years, and 2 years to <4 years.

3.1.1 Summarizing Categorical Variables

For categorical parameters, the number and percentage of subjects 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%.

3.1.2 Summary Statistics for Continuous Variables

For continuous parameters, descriptive statistics will include number of subjects with available measurements (n), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, and maximum, unless otherwise stated. For the primary efficacy variable and one of the secondary efficacy variables also a 95% CI will be presented. For PK parameters, the coefficient of variation (CV) and geometric mean may also be presented.

For reporting descriptive statistics of continuous parameters, the following rules will be applied:

- Number of observations "n" will be an integer
- Mean, SD, median, Q1, Q3 and upper and lower bound of 95% CI will use 1 additional decimal place compared to the original data
- Coefficient of variance (CV [%]) will be presented with 1 decimal place
- Minimum and maximum will have the same number of decimal places as the original value
- Mean and median changes from Baseline lower than the minimal displayable change will be displayed without sign (eg, -0.00 is displayed as 0.00)

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

3.1.3 Table Presentation

Tables will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

3.1.4 Listing Presentation

Listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately. These listings will be ordered by age category and site-/subject number.

The header information for listings related to safety assessments reflects Age Category, Region/Country/Site-/Subject Number, and Gender/Age/Race/Weight.

Subject data listings are presented with the same number of decimal places for all values within one parameter. The number of decimal places within a listing of a variable is determined by the minimum absolute value across all subjects and visits, unless specified differently for individual variables. The number of decimal places is chosen so that the minimum value has

- Three significant figures if <100
- One decimal place if ≥100

The number of decimal places is restricted to a maximum of as many decimal places as are available in the original data.

Date variables that were captured on a CRF are presented as documented without imputing incomplete dates. Imputed dates are listed separately.

3.2 General Study Level Definitions

3.2.1 Analysis Time Points

3.2.1.1 Relative Day

Relative day is only defined for subjects who received study medication.

The relative day for an assessment or start or end dates of events (eg, AEs) is calculated according to the following rules:

- The relative day 1 indicates the date of the first dose of study medication
- The relative day for an event on/after the day of first dose of study medication is calculated as:
  Assessment/Event date - date of the first dose of study medication +1
- The relative day for an event before the day of first dose of study medication is calculated as:
  Assessment/Event date - date of the first dose of study medication

In subject data listings the relative day is presented:

- The relative day 1 (without any prefix) indicates the date of the first dose of study medication

  The relative day for an event on/after the day of first dose of study medication and on/before last dose of study medication is calculated as:
  Assessment/Event date - date of the first dose of study medication +1, the relative day will be presented without any prefix.
- The relative day for an event before the day of first dose of study medication is calculated as:
  Assessment/Event date - date of the first dose of study medication, the relative day will be presented with a prefix "-" to indicate number of days before first dose of study medication
- The relative day for an event after the day of last dose of study medication is calculated as:
  Assessment/Event date - date of last dose of study medication, the relative day will be presented with a prefix "+" to indicate number of days since last dose of study medication

For incomplete dates, no relative day is calculated.

Note: Missing values for date of last administration of study medication are imputed as specified in Section 4.2.4.

3.2.1.2 End Date of the First/Second Period

A subject is regarded to have started/ended a period as described below. For this, the start dates and end dates of study periods for each subject are defined in the following sections.

3.2.1.2.1 Subjects enrolled prior to Protocol Amendment 3 who are not 48h video-EEG Failures and subjects enrolled according to Protocol Amendment 3

3.2.1.2.1.1 First period

Selection Period:

- Start: Day of Visit 1
- End:
  - Subject does not discontinue from study: 1 day before Visit 3, or
  - Subject discontinues from study: "Date of last contact with Subject" on "Study Termination, Screen Failure Packet" CRF.

Evaluation Period (only if subject does not discontinue before or at Visit 3):

- Start: Day of Visit 3
- End:

  First of:
  - Day of Visit 6, or
  - Day of first Early Discontinuation Visit.

For subjects who do not enter the Second Period:

Down-Titration Period (only when subject is not on minimum dose):

- Start: 1 day after Day of End of Evaluation Period
- End: Day of Last Early Discontinuation Visit; if Day of Last Early Discontinuation Visit is missing, the date of last dose of study medication will be used

Followed by

Safety Follow-Up Period (safety follow-up visit will take place when subject is 2 weeks off study drug, ie, on 0mg/kg dose):

- Start: 1 day after Day of End of Down-Titration Period or 1 day after Day of End of Evaluation Period
- End: Day of Safety Follow-Up Visit

3.2.1.2.1.2 Second Period

Maintenance period:

- Start: 1 day after Day of Visit 6
- End: First of:
  - Day of first Early Discontinuation Visit, or
  - Day of End of Study*

* Day of End of Study as determined by sponsor, connected to market approval or completion of development of LEV in subjects 1 month to <4 years

Down-Titration Period (only when subject is not on minimum dose):

- Start: 1 day after Day of End of Maintenance Period
- End: Day of Last Early Discontinuation Visit; if Day of Last Early Discontinuation Visit is missing, the date of last dose of study medication will be used

Followed by

Safety Follow-Up Period (safety follow-up visit will take place when subject is 2 weeks off study drug, ie, on 0mg/kg dose):

- Start: 1 day after Day of End of Down-Titration Period or 1 day after Day of End of Maintenance Period
- End: Day of Safety Follow-Up Visit

For subjects who did not discontinue from Maintenance Period:

- The end date will be captured on "study termination" CRF.
- No down-titration and Safety Follow-Up will be performed for these subjects.

3.2.1.2.2 Subjects enrolled prior to Protocol Amendment 3 who are 48h video-EEG Failures

3.2.1.2.2.1 First period

Selection Period:

- Start: Day of Visit 1
- End:
  - Subject dose not discontinue from study: 1 day before Visit 6, or
  - Subject discontinues from study: "Date of last contact with Subject" on "Study Termination, Screen Failure Packet" CRF.

3.2.1.2.2.2 Second Period

For 48h video-EEG failures, the data will be re-mapped according to Table 3-2 and will be included in the efficacy and safety analysis.

Dose Adjustment Period (only if subject does not discontinue at Visit 2):

- Start: Day of Visit 6
- End: First of:
  - Day of Visit 9, or
  - Day of first Early Discontinuation Visit

1. <u>For subjects who discontinued during the Dose Adjustment Period:</u>

Down-Titration Period (only when subject is not on minimum dose):

- Start: 1 day after Day of End of Dose Adjustment Period
- End: Day of Last Early Discontinuation Visit; if Day of Last Early Discontinuation Visit is missing, the date of last dose of study medication will be used

Followed by

Safety Follow-Up Period (safety follow-up visit will take place when subject is 2 weeks off study drug, ie, on 0mg/kg dose):

- Start: 1 day after Day of End of Down-Titration Period or 1 day after Day of End of Dose Adjustment Period
- End: Day of Safety Follow-Up Visit

2. For subjects who did not discontinue during the Dose Adjustment Period:

Maintenance Period:

- Start: 1 day after Day of Visit 9
- End: First of:
  - Day of first Early Discontinuation Visit, or
  - Day of end of study*
    * Day of end of study as determined by sponsor, connected to market approval or completion of development of LEV in subjects 1 month to <4 years

3. For subjects who discontinue from maintenance period:

Down-Titration Period (only when subject is not on minimum dose):

- Start: 1 day after Day of End of Maintenance Period
- End: Day of Last Early Discontinuation Visit; if Day of Last Early Discontinuation Visit is missing, the date of last dose of study medication will be used

Followed by

Safety Follow-Up Period (safety follow-up visit will take place when subject is 2 weeks off study drug, ie, on 0mg/kg dose):

- Start: 1 day after Day of End of Down-Titration Period or 1 day after Day of End of Maintenance Period
- End: Day of Safety Follow-Up Visit

4. For subjects who did not discontinue from Maintenance Period:

- The end date will be captured on "study termination" CRF.
- No down-titration and Safety Follow-Up will be performed for these subjects.

3.2.2 Schedule of Study Assessments

The study protocol gives the overall study schedule and the permissible intervals for these visits expressed as the number of days relative to Visit 3: Section 5.2 of protocol.

Subjects who were directly enrolled in the Second Period based on the protocol prior to Amendment 3 will also be included in the efficacy and safety analysis with remapping of visit numbers to correspond to the ones for subjects who enrolled in the First Period.

Table 3–1 presents the assessment schedule for subjects:

- who are enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures; or
- who are enrolled according to Protocol Amendment 3; or
- who are enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures

Table 3–1: Assessment Schedule

Study Visit	Target day*	Visit Window	Week number
Subjects: • **who are enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures or** • **who are enrolled according to Protocol Amendment 3**			
Evaluation Period			
Visit 3	Day 1		Week 0
Visit 4	Day 15	Day 11 to Day 19	Week 2
Visit 5	Day 29	Day 25 to Day 33	Week 4
Visit 6	Day 43	Day 39 to Day 47	Week 6
Maintenance Period			
Visit 8	Day 71	Day 64 to Day 78	Week 10
Visit 10	Day 99	Day 92 to Day 106	Week 14
Visit 11	Day 127	Day 120 to Day 134	Week 18
Visit 12	Day 155	Day 148 to Day 162	Week 22
Visit 13	Day 183	Day 176 to Day 190	Week 26
Visit 15	Day 267	Day 260 to Day 274	Week 38
Visit 16	Day 351	Day 337 to Day 365	Week 50
Visit 17	Day 435	Day 421 to Day 449	Week 62
Every 12 weeks			
Subjects: • **who are enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures**			
Dose Adjustment Period			
Visit 6	Day 1		Week 0
Visit 7	Day 15	Day 11 to Day 17	Week 2
Visit 8	Day 29	Day 25 to Day 33	Week 4
Visit 9	Day 43	Day 39 to Day 47	Week 6
Maintenance Period			
Visit 10	Day 57	Day 50 to Day 64	Week 8
Visit 11	Day 85	Day 78 to Day 92	Week 12
Visit 12	Day 113	Day 106 to Day 120	Week 16
Visit 13	Day 141	Day 134 to Day 148	Week 20
Visit 14	Day 183	Day 176 to Day 190	Week 26
Visit 15	Day 225	Day 221 to Day 232	Week 32
Visit 16	Day 309	Day 295 to Day 323	Week 44
Visit 17	Day 393	Day 379 to Day 407	Week 56
Every 12 weeks			

Table 3–1: Assessment Schedule

Study Visit	Target day*	Visit Window	Week number

Note: the day of the first dose of study medication is defined as Study Day 1, while the day before the date of first dose of study medication is defined as Study Day -1 (there is no Study Day 0).
* Day relative to first study drug intake

In the event that more than 1 assessment occurs within a given visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

Table 3–2 presents the mapping of Study Visits to Analysis Visits for subjects:

- who are enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures; or
- who are enrolled according to Protocol Amendment 3; or
- who are enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures

Analysis visits will be used for analysis of long-term safety and efficacy data.

Table 3–2: Analysis Visit Mapping Table

Analysis Visit	Week number	Relative day since first study drug intake	Analysis window	Subjects enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures; or subjects who are enrolled according to Protocol Amendment 3 Study Visit (Target day[1])	Subjects enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures Study Visit (Target day[1])
Retrospective Baseline[2]		-	2 weeks prior to Visit 1		
Baseline Period					
-1	-1	-9	-9 – 0	Visit 1 Visit 2[3]	Visit 1 Visit 2[3]
Evaluation/Dose Adjustment/Maintenance Period					
0[4]	0	1		Visit 3	Visit 6
1	2	15	2 – 22	Visit 4	Visit 7
2	4	29	23 – 36	Visit 5	Visit 8
3	6	43	37 – 50	Visit 6	Visit 9
4	8	57	51 – 64	-	Visit 10
5	10	71	65 – 78	Visit 8 (Day 71)	-
6	12	85	79 – 95	-	Visit 11 (Day 85)
7	15	106	96 - 116	Visit 10 (Day 99)	Visit 12 (Day 113)
8	18	127	117 – 137	Visit 11 (Day 127)	-
9	21	148	138 – 158	Visit 12 (Day 155)	Visit 13 (Day 141)
10	24	169	159 – 179	-	-
11	27	190	180 – 200	Visit 13 (Day 183)	Visit 14 (Day 183)
12	30	211	201 – 231	-	Visit 15 (Day 225)
13	36	253	232 – 295	Visit 15 (Day 267)	-
14	48	337	296 – 379	Visit 16 (Day 351)	Visit 16 (Day 309)
15	60	421	380 – 463	Visit 17 (Day 435)	Visit 17 (Day 393)

16	72	505	464 – 547	Visit 18 (Day 519)	Visit 18 (Day 477)
17	84	589	548 – 631	Visit 19 (Day 603)	Visit 19 (Day 561)
Every 12 weeks					
Down-titration Period					
EDV/EOS	-	-			
Safety Follow-Up Period					
Safety Follow-Up	-	-			

EDV= Early Discontinuation Visit; EOS= End of Study
[1] Day relative to first study drug intake
[2] Retrospective Baseline is only applicable to seizure count data. For other analyses the time window of "2 weeks prior to Visit 1" for baseline is not applied.
[3] Study Visit 2 is only applicable for those subjects enrolled prior to Protocol Amendment 3.
[4] Analysis visit 0 is not applicable to laboratory test, since Week 0 is not scheduled for them.

In the event that more than 1 assessment occurs within a given analysis visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

3.2.3 Unscheduled Visits

If not otherwise stated, data from unscheduled visits are:

- Not considered for by-visit presentations
- Considered for a respective period depending on the date when the unscheduled visit occurred
- Presented in subject data listings

3.2.4 Mapping of Assessments Performed at Early Discontinuation Visit

Efficacy and safety assessments at an Early Discontinuation Visit (EDV) that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. In the event that the subject discontinues between two scheduled visits the data from the EDV are presented with data corresponding to the next scheduled visit for the subject. For subjects who had more than one EDV because of the starting dose of the Down-Titration Period, only the first EDV will be mapped to the scheduled visit.

3.2.5 Age

3.2.5.1 Chronological Age

For a given date, chronological age in months is defined as: (Date – Date of birth) / 30.4375, assuming that the date difference is given in days.

3.2.5.2 Adjusted Age

Pre-Term birth will be accounted for by using the adjusted age which is defined as

- [(Date – Date of Birth) – (36 – number of weeks pre-term) x 7] / 30.4375
  for subjects of chronological age < 12 months and
- Chronological age, otherwise

If not specified otherwise, adjusted age at the date of the assessment is used for all analyses.

3.2.5.3 Age at Entry Into Study

The adjusted age at entry into study is defined as the adjusted age at the screening date. This is also referred to as "Age at entry into study"

3.2.6 Body Mass Index

Body Mass Index (BMI) will be calculated using the formula:

$BMI = weight\ (kg) / (height\ (m))^2$.

3.2.7 Exposure to Study Medication

The date of first dose of study medication is defined as the first study medication dose date according to the First Administration CRF.

The date of last dose of study medication is defined as the last dose of study medication reported on the standard Trial Termination CRF.

The number of days of exposure is defined as the stop date minus the treatment start date +1 day. Days with unknown or zero dosing which occur prior to the last dose of study medication in the study will be included in the calculation.

3.3 Definition of Baseline Values

For by-visit analysis, baseline is defined as following:

For efficacy variables (except partial seizure frequency collected from DRC), safety variables, laboratory variables (blood chemistry, hematology), vital signs, and body weight, baseline is defined as the last value prior to the first dose of study medication (LEV).

In general: Change from Baseline (CfB) is calculated as:
CfB = Post-Baseline value – Baseline value.

If not noted otherwise, change from Baseline is calculated for post Baseline visits according to the visit schedule including unscheduled visits and for Last Visit.

For percent reduction in partial seizure frequency by DRC, a baseline value is calculated from retrospective baseline period + selection period.

For by-analysis visit, baseline is calculated from Analysis Visit Baseline value.

3.4 Protocol Deviations

After all CRFs have been retrieved and entered, all queries issued and answered to the extent possible, and prior to locking the database, a final Data Evaluation Meeting (DEM) will be held.

The meeting covers but is not limited to the following tasks:

- Review and assessment of important protocol deviations
- Agreement/confirmation of data handling rules
- Evaluation of statistical methodology

Important protocol deviations are to be classified into important for:

- Efficacy
- Conduct/Patient Management

Criteria and rules for the identification and classification of important protocol deviations regarding their impact on study conduct/subject handling and/or the assessment of efficacy are to be setup and to be minuted. Decisions made during the meeting are minuted.

3.5 Analysis Sets

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:
  - SS_A (Safety Set [Adjunctive therapy])
  - SS_M (Safety Set [Monotherapy])
- Full Analysis Sets:
  - FAS_A (Full Analysis Set [Adjunctive therapy])
  - FAS_M (Full Analysis Set [Monotherapy])
- Pharmacokinetic Per-Protocol Set (PK-PPS)
  - PK-PPS_A [Pharmacokinetic-Per-Protocol Set (Adjunctive therapy)]
  - PK-PPS_M [Pharmacokinetic-Per-Protocol Set (Monotherapy)]

If not stated otherwise, presentation of:

- Disposition and important protocol deviations are based on the ES
- Demographics, other baseline characteristics, safety, and exposure data are based on the SS_A and SS_M
- Efficacy data are based on the FAS_A and FAS_M.

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects enrolled (which include all subjects screened) into the Selection Period.

3.5.2 Safety Set

The SS_A will include all enrolled subjects on adjunctive therapy who receive at least 1 dose of study medication in the Evaluation Period.

The SS_M will include all enrolled subjects on monotherapy who receive at least 1 dose of study medication in the Evaluation Period.

For subjects who were directly enrolled in the Second Period based on the protocol prior to Amendment 3, after re-mapping they will be considered as entering in the Evaluation Period if they receive at least 1 dose of study medication in the Dose Adjustment Period.

3.5.3 Full Analysis Set

The FAS_A will consist of all subjects in the SS_A who have at least 1 post-baseline efficacy assessment.

The FAS_M will consist of all subjects in the SS_M who have at least 1 post-baseline efficacy assessment.

3.5.4 Per Protocol Set

Not applicable.

3.5.5 Other analysis sets

The PK-PPS_A will consist of all subjects in the SS_A for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

The PK-PPS_M will consist of all subjects in the SS_M for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

3.6 Treatment Assignment and Treatment Groups

This is an open-label study with a single treatment arm; hence subjects will not be randomized.

3.7 Center pooling strategy

No pooling of centers is planned for this study.

3.8 Coding dictionaries

Medical history and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 that is released for execution at UCB/Designee. Medication including anti-epileptic drugs (AEDs) will be coded using the World Health Organization Drug Dictionary (WHO-DD) WHO-DD SEP/2017 that is released for execution at UCB/designee. The applied version of the dictionaries will be explicitly mentioned in the respective tables and listings.

3.9 Changes to protocol-defined analyses

Not applicable.

3.10 Consideration for COVID-19

Since the target population of this study is infants or young children in which the population is not considered will be impacted on the efficacy and safety evaluation due to COVID-19. No additional amendment to CRF or analyses is required.

4 STATISTICAL ANALYTICAL ISSUES

4.1 Adjustments for Covariates

This section is not applicable for this study.

4.2 Handling of Dropouts or Missing Data

Days with missing seizure data will not be used for the calculation of seizure frequency per week. If subjects drop out, their seizure counts over the available period will be used and transformed into seizure frequency per week, by dividing the number of seizures during the available period by the number of days of that period, multiplied by 7.

Safety variables will be analyzed insofar as they are available, without imputation or carrying values forward.

Imputations for missing or partial values for dates for AEs and concomitant medications will be applied to determine if an event is to be considered treatment-emergent or concomitant. Across safety and PK analyses, only reported data will be used.

4.2.1 General Imputation Rule for Incomplete Dates

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

- Start and stop dates of concomitant medication, Section 4.2.2
- Start and stop dates of Adverse Events, Section 4.2.3

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

4.2.2 Handling of Incomplete Dates in Context of Concomitant Medications

Any medications with incomplete start and/or end dates will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the eCRF.

Imputation of Partial Start Dates:

- If only the month and year are specified and the month and year of first dose of study medication are 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 of study medication are the same as the month and year of the start date, then use the date of first dose of study medication
- If only the year is specified, and the year of first dose is not the same as the year of the start date of study medication, 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 of study medication
- 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 of study medication

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.

4.2.3 Handling of Adverse Events with Missing Data

Any AEs with incomplete onset and outcome (end) dates/times will be handled according to the following rules for classification as treatment-emergent. Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

Imputation of Partial Onset Dates:

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

Imputation of Partial End 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
- If the onset time of the event is unknown, impute it as 00:00 unless the known part of the onset date is the same as the date of first dose of study medication; in this case impute the time of first dose of study medication

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to study medication per the investigator will be assumed to be related.

Data handling for worsened AEs is provided below. The standard AE CRF has the outcome of "worsened" to be used when there is an increase in the intensity of an AE. The definition of "worsened" is when the AE is still present but at a heightened intensity. CRF instructions dictate to complete a new AE screen with the event term of the worsened event.

Note that the outcome of "worsened" is not allowed terminology within the CDISC standards. In the SDTM.AE, the data is mapped to the outcome "Not Recovered/Not Resolved". The outcome of "Worsened" will be kept in SDTM.SUPPAE. For subject data listings, the convention will be to use the mapped SDTM terminology of "Not Recovered/Not Resolved".

4.2.4 Handling of Study Medication with Missing data

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

If a subject has missing last administration information from the Study Termination CRF page, the last available treatment date with nonzero total daily dose from Drug Dosing Log will be used for last administration date if it is not the same as the first administration date of the subject. If the subject does not have any available treatment date or the last available treatment date is the same as the first administration date from Drug Dosing Log and is missing last administration information from the Study Termination CRF page, the last contact date from CRF is used for the last administration date.

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.

4.3 Interim Analyses and Data Monitoring

No formal interim analysis is planned for this study. For regulatory purposes, two planned data cut-offs will be made when the final subject who completes the Evaluation Period reaches Visit 13 and Visit 16 in order to obtain 6-month and 12-month exposure data, respectively. All the efficacy and safety analysis planned in the protocol will be performed for NDA submission using the interim cut-off data followed by additional cut-off and/or final analysis for long-term follow-up evaluation.

In addition to above, an interim analysis (IA) was performed for providing PMDA with the latest information to discuss if the study can be discontinued and the application method can be changed to extrapolation strategy based on the results of the IA, which is based on the suggestion at the consultation meeting with PMDA held on [redacted] The IA was performed according

to the eCRF snapshot on 04 Jun 2021, in which the data cut-off date was 30 Apr 2021.

4.4 Multicenter Studies

Since it is expected that there will be only a few subjects per age category and center combination, there are no plans to summarize data by age category and center. Summary tables will be presented pooled for all centers.

4.5 Multiple Comparisons/Multiplicity

If the primary analysis of the primary variable (median percent reduction for adjunctive therapy) at Study Visit 6 is not significant, the statistical testing will stop. If testing at Study Visit 6 is significant, the analysis will be repeated for Study Visit 4. If testing at Study Visit 4 is also significant, the analysis will be repeated for Study Visit 5. In that case, the second and the third analyses are also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed.

4.6 Use of an Efficacy Subset of Subjects

No additional efficacy subset is used.

4.7 Active-control studies intended to show equivalence

No comparator and no testing for equivalence in this study, hence this section is not applicable for this study.

4.8 Examination of Subgroups

In this study 4 age categories will be investigated: 1 month to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <4 years. For the primary efficacy variable the data of the two youngest age categories will be pooled and data of the primary efficacy variable will be summarized by the so-obtained 3 age-categories and overall.

Note: for the age classification, the age at entry into study is used (Section 3.2.5.3).

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject Disposition

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

Disposition related tables cover a presentation of screen failure reasons, frequencies of completed and discontinued subjects including reason for discontinuation overall and by video-EEG status (video-EEG failures and video-EEG non-failures for subjects enrolled prior to Protocol Amendment 3 and subjects enrolled following Protocol Amendment 3), attendance at visits and periods, study duration as well as analysis sets. In addition, information on number of subjects enrolled (ie, Enrolled Set), and being in the Safety Sets, Full Analysis Sets, and

Pharmacokinetic Per-Protocol Sets is presented overall and by investigator site together with the date of first subject in and last subject out.

The following listings will be provided: study eligibility criteria text; subjects who did not meet study eligibility criteria; subject disposition; study discontinuation; visit dates; study periods; and subject analysis sets.

5.1.1 Definitions and Derivations

5.1.1.1 Subject Status

Subject status regarding completion is taken from the Study Termination CRF.

5.1.1.2 Last Administration of Study Medication

Missing values for date of last administration of study medication are imputed as specified in Section 4.2.4.

5.1.1.3 Time to Discontinuation from Study

An event in the sense of the variable Time to Discontinuation from Study is observed if for a subject on the Study Termination CRF Subject status at study termination is “Dropout”.

In case of an event,
Time to Discontinuation from Study [months] =
12 x (Date of premature study termination [Study Termination CRF] -
date of enrolment) / 365.25.
This observation is not censored.

In case of no event,
Time to Discontinuation from Study [months] =
12 x (Date of last visit – date of enrolment) / 365.25.
This observation is censored.

5.1.1.4 Period Started/Ended

A subject is regarded to have started / ended period as described in Section 3.2.1.2.

5.1.1.5 Duration of a Period

The duration of a period is not shown in context of disposition. The duration of a period is used as the duration of exposure to study medication, see Section 3.2.7.

5.1.2 Tables

A table Reasons for Screen Failures for the ES presents, for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Number of screened subjects and number and percentage of screen failures.
- Number and percentage of screen failures by primary reason for screen failure.

The table is presented for subjects across all age categories.

A table Disposition of Subjects Screened for the ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Number of subjects screened, treated, being in the FAS_A, FAS_M, SS_A, SS_M, and PK-PPS_A and PK-PPS_M , by age category and for all subjects
- The date of first subject in (defined as date of first screening visit) and last subject out (defined as date of last visit for the last subject)

Subject disposition is presented for subjects across all age categories by investigator site and overall.

A table Disposition and Discontinuation Reasons for SS presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Number and percentage of subjects who started and completed the study
- Number and percentage of subjects discontinuing the study including primary reason for discontinuation

For the whole table, percentages are based on the number of the SS.

Subject disposition and the reason for discontinuation is presented overall and by study period.

Also number and percentage of subjects continuing treatment after the study is presented.

A table Attendance at Analysis Visits for the SS presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Number and percentage of subjects at a visit

A table Disposition of Analysis Sets presents for the ES the frequency distribution (number and percentage of subjects) per analysis set, ie,:

- For subjects on adjunctive therapy:
  - ES
  - SS_A
  - FAS_A
  - PK-PPS_A

and

- For subjects on monotherapy:
  - ES
  - SS_M
  - FAS_M
  - PK-PPS_M

5.1.3 Listings

A listing Study Eligibility Criteria Text (for the ES[1]) presents:

- Protocol/Amendment Number
- Criteria/Number
- Description

[1] Analysis set is specified only for technical reasons as content-wise this is unnecessary..

A listing Therapy presents:

- Site-/Subject Number
- Therapy

A subject data listing Subjects Who Did Not Meet Study Eligibility Criteria for the ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, for subjects that do not comply with at least one study eligibility criteria:

- Age Category
- Site/Subject Number
- Protocol dated
- Protocol/Amendment Number
- Inclusion Criteria Not Met
- Exclusion Criteria Met

A subject data listing Subject Disposition for the ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Protocol/Amendment Number
- Age Category
- Site/Subject Number
- Subject Status
- Date of Informed Consent
- Date of First Study Medication/Last Study Medication including relative day/Imputed Last Study Medication including relative day
  Note: Imputation rule for missing Last Study Medication date is given in Section 4.2.4.
- Date of Premature Study Termination/Final Contact (For screen failure subjects, this is the date of screen failure.)
- Primary Reason for Premature Study Termination (For screen failure subjects, this is the reason for screen failure.)

A subject data listing Study Discontinuation for ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, for subjects who discontinued the study the reason for discontinuation including:

- Protocol/Amendment Number
- Age Category
- Site/Subject Number
- Reason for Discontinuation
- Period
- Dose from which was discontinued
- Days on dose from which was discontinued
- Total Days on Study Medication

A subject data listing Visit Dates for ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, visit dates including:

- Age Category
- Site/Subject Number
- Visit
- Analysis Visit
- Visit Date
- Relative Day

A subject data listing Study Periods for ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Period
- Start Date Period
- End Date Period

A subject data listing Subject Analysis Sets for the ES presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, the analysis set that a certain subject belongs to:

- For subjects on adjunctive therapy
  - Age Category
  - Site/Subject Number
  - ES

  - SS_A
  - FAS_A
  - PK-PPS_A
- For subjects on monotherapy
  - Age Category
  - Site/Subject Number
  - ES
  - SS_M
  - FAS_M
  - PK-PPS_M

5.2 Protocol Deviations

Prior to database lock, protocol deviations will be assessed if important or not important and if included into the relevant analysis set according to predefined specifications.

5.2.1 Analysis Summary

Important protocol deviations (IPD) defined in the protocol-specific document, and additionally identified at the data evaluation meetings, will be listed. In addition, the number and percentage of subjects with at least one important protocol deviation will be summarized overall and by category of important protocol deviation for the ES. The number and percentage of subjects with no important protocol deviations will also be summarized for the ES. These will be summarized by age category and for all subjects combined. A listing of important protocol deviations will be provided.

5.2.2 Definitions and Derivations

The category, type, description, and action resulting from important protocol deviations are derived in accordance with the Specifications of Important Protocol Deviations document and decisions made on the DEM.

5.2.3 Tables

A table Important Protocol Deviations presents, for subjects on adjunctive therapy and for subjects on monotherapy, separately, the number and percentage of subjects with:

- No important protocol deviation
- At least one important protocol deviation

Percentages are based on the number of subjects in the ES, whereby subjects can have more than 1 important protocol deviation.

5.2.4 Listings

A subject data listing Important Protocol Deviations presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, for subjects with at least 1 important protocol deviation the following information:

- Protocol/Amendment Number
- Age Category
- Site/Subject Number
- Start Date of Deviation (if applicable)
- Deviation Category (efficacy, conduct/patient management)
- Deviation Type (eg, inclusion criteria, exclusion criteria, treatment non-compliance)
- Deviation Description (giving details)

Deviation category, deviation type, deviation description and action are in accordance with the IPD.

A subject data listing Subjects Excluded from Efficacy Analysis presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, the following information:

- Age Category
- Site/Subject Number
- Excluded from Analysis Set
- Reason for Exclusion from Analysis Set

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

6.1 Demographics

The variables to be considered are:

- Age at entry into study (as defined in Section 3.2.5.3) – continuous and categorized as: 1 month to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <4 years
- Gender
- Weight (kg)
- Height (cm)
- BMI (kg/m^2) (as defined in Section 3.2.6)
- Ethnicity

- Race (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other/Mixed)
- Ethnic subgroup (Japan, Other)

6.1.1 Definitions and Derivations

For definition of age, see Section 3.2.5.

6.1.2 Tables

A table Demographics presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics on age at entry into study, weight, height, BMI
- Frequency distribution (number and percentage of subjects) for age (1 month to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <4 years)
- Frequency distribution (number and percentage of subjects) on gender, race and ethnic subgroup

Missing is presented as category only if this is applicable for a certain variable.

6.1.3 Listings

A subject data listing Demographics presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Date of Birth
- Age at entry into Study
- Adjusted Age
- Gender
- Race
- Ethnicity
- Ethnic subgroup
- Height
- Weight
- BMI

6.2 ECG and CT Scan / MRI

A CT scan or MRI will be performed only for those subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have

changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.

6.2.1.1 Definitions and Derivations

Not applicable.

6.2.1.2 Tables

A table CT/MRI Interpretation at Baseline presents, for subjects on adjunctive therapy and for subjects on monotherapy, separately, a frequency distribution (number and percentage of subjects) for:

- CT/MRI (CT performed; MRI performed; Not performed)
- CT/MRI Result (Normal; Abnormal, not clinically significant; Abnormal, clinically significant; Not performed)

6.2.1.3 Listings

A subject data listing CT Scan/MRI presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Was CT scan / MRI image taken
- Type of Image (CT/MRI)
- Date/Relative Day of Image
- Result of Image

A subject data listing Baseline ECG Interpretation presents:

- Age Category
- Site/Subject Number
- Date/Relative Day of ECG
- Result of ECG

6.3 Neurological Examination

A complete neurological examination will be performed at the Screening Visit according to the protocol schedule of study assessments. The complete neurological examination will include selected assessment of general neurological status (level of consciousness, mental status, speech), cranial nerves, reflexes, motor system (general motor status, muscle strength, muscle tone), coordination/cerebellar function, and sensation.

Clinically significant neurological findings will be reported as AEs. Also, any change to clinically significant neurological findings that was not the same at baseline will be provided.

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

6.3.1.1 Definitions and Derivations

Not applicable.

6.3.1.2 Tables

Not applicable.

6.3.1.3 Listings

A listing Neurological Examination presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, for each abnormal finding noted during neurological examinations:

- Age Category
- Site/Subject Number
- Visit
- Date/Relative Day
- Abnormality as domain concatenated with the examination parameter that led to the abnormal finding
- Clinical Significance

6.4 Physical Examination

A complete physical examination will be performed at the Screening Visit according to the protocol schedule of study assessments.

6.4.1.1 Definitions and Derivations

Not applicable.

6.4.1.2 Tables

None.

6.4.1.3 Listings

A listing Physical Examination Abnormalities presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, for each abnormal finding noted during physical examination:

- Age Category
- Site/Subject Number
- Visit Done/Not done
- Date/Relative Day
- Abnormality
- Clinical Significance

6.5 Other Baseline characteristics

Subject data listings are presented for other baseline characteristics data of lifestyle, pre-term birth status and family medical history.

6.5.1.1 Definitions and Derivations

Not applicable.

6.5.1.2 Tables

None.

6.5.1.3 Listings

A listing Lifestyle Status presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Did the Subject use alcohol within the past 6 months
- Did the Subject use illicit drugs within the past 6 months

A listing Pre-Term Birth Status presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Was Subject Pre-Term Infant
- If Yes, Number of Weeks Pre-Term

A listing Family Medical History presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- System Organ Class
- Preferred Term
- Reported condition
- Start date and stop date of reported condition.

6.6 Epilepsy Background Variables

Epilepsy related tables will present summary statistics for: diagnosis of epilepsy (age at onset, duration of epilepsy at study entry, historical seizure counts overall and by seizure type) as well as frequency distributions for etiology, and ILAE seizure classification.

In addition, the interpretation of baseline EEG and CT/MRI (normal, not clinically relevant abnormal, and clinically relevant abnormal) will be presented.

Details on epilepsy related information are provided in subject data listing.

6.6.1 Definitions and Derivations

6.6.1.1 Epilepsy Duration and Age at Onset

Date of first onset of epilepsy is documented in the Diagnosis of Epilepsy CRF. Based on this date, the duration of epilepsy and the age at onset is derived as followers:

- Epilepsy duration [months] = (date of Visit 1 – date of first seizure) / 30.4375
- Age at onset of epilepsy [months] = (date of first seizure – date of birth) / 30.4375.

6.6.1.2 Historical partial onset seizures and seizures of subtypes IA, IB, and IC during 2 weeks prior to Visit 1

The information if a subject experienced any seizures (note: this includes seizures other than partial onset seizures) is captured in the Historical Seizure Count CRF.

A subject is regarded as having experienced any simple partial seizures (subtype IA) during the past 2 weeks to Visit 1, if the number of simple partial seizures in the Historical Seizure Count is >0 for the past 2 weeks prior to Visit 1, otherwise the subject is regarded as not having experienced simple partial seizures during the past 2 weeks prior to Visit 1.

Analogously, this is done for:

- Experiencing complex partial seizures (subtype IB) during the past 2 weeks prior to Visit 1
- Experiencing partial evolving to secondarily generalized seizures (subtype IC) during the past 2 weeks prior to Visit 1
- Experiencing Generalized seizures (subtype II) during the past 2 weeks prior to Visit 1
- Experiencing unclassified epileptic seizures (subtype III) during the past 2 weeks prior to Visit 1.

6.6.1.3 Historical Partial Onset Seizures (Type I) During 2 Weeks Prior to Visit 1

A subject is regarded as having experienced any partial onset seizures (any subtype) during the past 2 weeks prior to Visit 1, if they experienced any simple partial seizures (subtype IA), complex partial seizures (subtype IB) or partial evolving to secondarily generalized seizures (subtype IC) during the past 2 weeks prior to Visit 1, otherwise they are not regarded as having had any partial onset seizures during the past 2 weeks prior to Visit 1.

6.6.1.4 Historical Seizure Count for Partial Onset Seizures During 2 Weeks Prior to Visit 1

The information regarding ILAE historical seizure count is captured on the “ILAE Seizure Classification History” CRF.

The number of simple partial seizures (subtype IA), number of complex partial seizures (subtype IB) and number of partial evolving to secondarily generalized seizures (subtype IC) during 2 weeks prior to Visit 1 is captured in the Historical Seizure Count CRF.

The number of partial onset seizures (any subtype) during the past 2 weeks prior to Visit 1 will be derived as the sum of the number of:

- Simple partial seizures during the past 2 weeks prior to Visit 1
- Complex partial seizures during the past 2 weeks prior to Visit 1
- Partial evolving to secondarily generalized seizures during the past 2 weeks prior to Visit 1

6.6.2 Tables

A table Diagnosis of Epilepsy presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics for age (months) at onset of epilepsy
- Summary statistics for duration (months) of epilepsy at study entry

A table ILAE Seizure Classification History presents a frequency distribution (number and percentage of subjects) for:

- Partial onset seizures (I), Total and in ILAE sub-classes as specified in the CRF (seizure description and ILAE seizure code) (eg, Simple partial (IA), Complex partial (IB), …)
- Generalized seizures (II), Total and in ILAE sub-classes
- Unclassified epileptic seizures (III)

A subject can appear in more than 1 category.

A table Historical Seizure Count, Number and Percentage of Subjects presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Frequency distribution (number and percentage of subjects) for experiencing any seizure during the 2 weeks prior to Visit 1
- Frequency distribution (number and percentage of subjects) for experiencing any partial onset seizures
- Frequency distribution (number and percentage of subjects) for experiencing partial onset seizure subtypes (simple partial, complex partial, partial evolving to secondarily generalized)
- Frequency distribution (number and percentage of subjects) for experiencing any generalized seizures
- Frequency distribution (number and percentage of subjects) for experiencing any unclassified epileptic seizures

A table Historical Seizure Count, Descriptive Statistics presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics for the number of any seizures during the 2 weeks prior to Visit 1

- Summary statistics for the number of partial onset seizures
- Summary statistics for the number of partial onset seizure subtypes (simple partial, complex partial, partial evolving to secondarily generalized)
- Summary statistics for the number of generalized seizures
- Summary statistics for the number of unclassified epileptic seizures

A table Classifications of Epileptic Syndromes presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, a frequency distribution (number and percentage of subjects) for:

- Localization related classifications (with subdivisions)
- Generalized classifications (with subdivisions)
- Epilepsies and syndromes undetermined (with subdivisions)
- Special syndromes

6.6.3 Listings

A subject data listing Diagnosis of Epilepsy presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Date of first diagnosis
- Age at first diagnosis
- Duration of epilepsy at study entry
- History of status epilepticus requiring hospitalization during the 30 days prior to Visit 1, except for status epilepticus occurring during the first 10 days of life
- Diagnosis of epilepsy with partial onset seizures whether or not secondarily generalized
- History of epilepsy secondary to progressing cerebral diseases
- Treatable seizure etiology (ie, febrile seizures)
- Current diagnosis of Rasmussen's syndrome, Landau-Kleffner disease or Lennox-Gastaut syndrome

A subject data listing ILAE Seizure Classification History presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Ever Experienced a Seizure or a Cluster
- Description (Partial onset seizures, Generalized seizures, Unclassified epileptic seizures)/Subtype Description

- ILAE Seizure Code (IA, IB, IC, other)

A subject data listing Historical Seizure Count presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Any seizures during the 2 weeks prior to Visit 1
- Number of seizures during the 2 weeks prior to Visit 1
- Number of seizures of ILAE class IA, IB, IC, during the 2 weeks prior to Visit 1

A subject data listing Classifications of Epileptic Syndromes presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Classification of Epileptic Syndromes
- Sub-Classification of Epileptic Syndromes

A subject data listing Classification of Epileptic Syndromes – Details on Generalized Syndromes presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Classification of Generalized Epileptic Syndrome
- Details on Generalized Syndrome
- Result

6.7 Medical History and Concomitant Diseases

Tables are presented separately for past diseases and concomitant diseases. The number and percentage of subjects with diseases will be summarized by age category, for subjects on adjunctive therapy only, overall and by system organ class (SOC) and preferred term (PT) on the SS_A and on the SS_M.

Tables will be sorted alphabetically by SOC and within SOC by descending frequency of PT for the "all subjects combined" group in all subjects group.

Data on "Family members who experienced any previous or ongoing DILI- relevant medical conditions or have any DILI-relevant inheritable disorders" will be summarized in the same way as for past diseases.

The following listings will be provided: previous and ongoing medical history glossary, and previous and ongoing medical history conditions.

6.7.1 Definitions and Derivations

Medical conditions at study entry are documented on the Medical History CRF and are to be categorized as past or concomitant:

- Past diseases: Medical conditions which are not specified as ongoing (response to item "Ongoing?"="No")
- Concomitant diseases: Medical conditions which are specified as ongoing ("Ongoing?"="Yes") or missing status information

Start and stop date are documented partially with month and year only. No date imputation is foreseen.

6.7.2 Tables

A table Past Medical History Conditions (except epilepsy) presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Any Medical Condition
  Number and percentage of subjects reporting at least one medical condition.
- By System Organ Class
  Number and percentage of subjects reporting at least one medical condition within a SOC.
- By Preferred Term
  Number and percentage of subjects reporting at least one medical condition of that PT within its SOC.

The table is repeated for:

- Concomitant Diseases (except epilepsy)

No table is presented for Procedure History.

6.7.3 Listings

A listing Previous and Ongoing Medical History Glossary – All Conditions represents the mapping of reported terms to preferred terms and system organ class based on the MedDRA coding dictionary:

- System Organ Class
- Preferred Term
- Reported Abnormality/Symptom

A subject data listing Previous and Ongoing Medical History Conditions presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- System Organ Class/Preferred Term
- Reported Condition

- Information about the condition being past or concomitant
- Start Date/Stop Date

A subject data listing Procedure History presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Procedure (Reported Term)
- Date of Procedure

6.8 Prior and Concomitant Medications

Tables present past AEDs, past Non-AEDs, concomitant AEDs, and concomitant Non-AEDs, separately.

Past and concomitant non AED medications are coded with WHO-DD, and will be summarized by Anatomical Main Group (ATC level 1), Pharmacological Subgroup (ATC level 3) and preferred term, by age category and for all subjects combined for the SS_A and for the SS_M.

Past and concomitant AED medications are also coded with WHO-DD, and will be summarized by Chemical Subgroup (ATC level 4) and preferred term, by age category and for all subjects combined for the SS_A and for the SS_M.

The following listings will be provided: prior and concomitant medications non-AEDs, glossary of prior and concomitant non-AED medications with verbatim term coded into ATC levels 1 and 3, prior and concomitant medications AEDs, glossary of prior and concomitant AED medications with verbatim term coded into ATC level 4 and preferred term.

6.8.1 Definitions and derivations

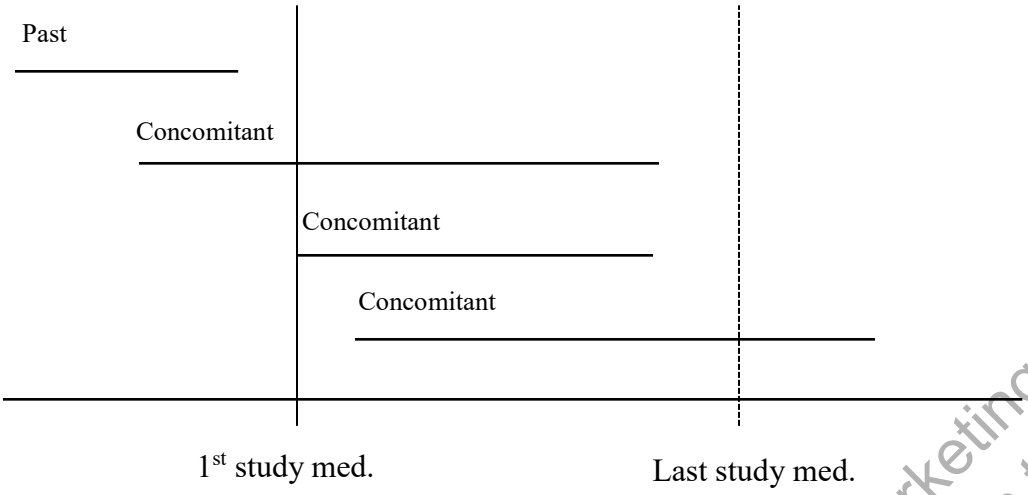
Medications documented on the Prior and Concomitant Medications CRF and are categorized as follows (see Figure 6.1):

- Past medication
  Medication that stopped prior to the first dose of study medication.
- Concomitant medication
  Medication with at least 1 day in common with the dosing period, ie, either
  - starts before first dose of study medication and is ongoing at day of first dose of study medication

    OR
  - starts on or after first dose of study medication

  Medication with a missing start date and missing information regarding “ongoing” status and medication with a missing start and missing end date are conservatively considered “concomitant”.

Figure 6–1: Past and Concomitant Medication



Past or concomitant medication is assigned to each study period the subject goes through based on the start and end date of the past or concomitant medication. For the definitions of study periods, please refer to Section 2.3.1. If intake is documented outside of any study period defined in Section 2.3.1, then for this part the period is given as "Not applicable" in the period column of the corresponding listings.

Identification of AEDs

Medications are regarded as potential AED if they meet one of the following criteria:

- On the Prior and Concomitant Medications CRF the item "Core AED?" is checked
- The medication is documented on the History of Previous Antiepileptic Drug Treatment CRF module

Based on the criteria above, UCB will perform the manual review to the name, frequency and formulation of the medications and to identify the AEDs in an external file which is regularly updated in the course of the study.

Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Concomitant AEDs are captured on the Prior and Concomitant Medications (AEDs and non-AEDs) eCRF. Concomitant AEDs will be summarized separately by level 4 ATC code and preferred medication name. If a medication identified as an AED does not code to a level 4 ATC code, the highest level of coding will be displayed along with the preferred drug name. Summaries of AEDs will be presented separately from other concomitant medications by infusion duration and overall.

Handling of prior and concomitant medications missing data is described in the Section 4.2.2.

6.8.2 Tables

For non-AEDs, tables are sorted alphabetically by Anatomical Main group (ATC level 1) and Pharmacological Subgroup (ATC level 3) and within level 3 by descending frequency of PT in the all subjects group.

For AEDs, tables are sorted alphabetically by Chemical Subgroup (ATC level 4) and within level 4 by descending frequency of preferred term in the all subjects group.

The following tables will be provided:

- Past Anti-Epileptic Drugs
- Concomitant Anti-Epileptic Drugs
- Anti-Epileptic Drugs at Study Visit 1
- Past Medications (Non-AEDs)
- Concomitant Medications (Non-AEDs)

6.8.3 Listings

A listing Medication Glossary represents the mapping of reported terms to preferred terms and WHO-DD coding.

- Anatomical Main Group, Level 1
- Pharmacological Subgroup, Level 3
- Preferred Term
- Reported Term
- AED Flag

A subject data listing Past and Concomitant Medications (Non AEDs) presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Anatomical Main Group (Level 1)/Pharmacological Subgroup (Level 3)/Preferred Term/Reported Term
- Dose per Intake and Unit
- Frequency/Formulation
- Indication
- Past / Concomitant medication
- Start Date (Relative Day)/Stop Date (Relative Day)

This listing is repeated for:

- Concomitant Anti-Epileptic Drugs

- Changes in Concomitant AEDs – AEDs that started on or after First Dose of Study Medication

A subject data listing Past Anti-Epileptic Drugs presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Anatomical Main Group (Level 1)/Pharmacological Subgroup (Level 3)/Preferred Term/Reported Term
- Maximum Daily Dose and Unit
- Start Date (Relative Day)/Stop Date (Relative Day)
- Reason for Discontinuation

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

7.1 Definitions and Derivations

Since derivations for compliance is connected to derivations for exposure, derivation to both topics are described here.

Date of first dose of study medication is documented in the "First Administration" CRF.

Missing values for date of last administration of study medication are imputed as specified in Section 4.2.4.

Details on study medication administration are recorded on the CRFs: First Administration; Study Medication Administration – Dry Syrup; and Study Medication Administration – IV.

Overall compliance with Levetiracetam, administered once in the morning and once in the evening, will be examined for subjects whose total study medication administration and first and last days of treatment in the first and/or second period are known:

- First Period, Treatment compliance (%) will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\sum_{first\ day}^{last\ day}(\#\text{ of actual administrations per day})}{\text{total \# of administrations planned during the first period}} \text{ x } 100$$

  where "total # of administrations planned during the first period" is equal to the total number of administrations planned during first administration of study medication to last planned administration in Evaluation Period, or day of discontinuation, which will be calculated as the duration of Evaluation Period in days ×2. In consideration of whether the first administration is taken in the morning or in the evening, please see Section 10.1.1.

- Second Period, Treatment compliance (%) will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\sum_{first\ day}^{last\ day}(\text{\# of actual administrations per day})}{\text{total \# of administrations planned during the time the subject was in second period}} \text{ x } 100$$

where "total # of administrations planned during the time the subject was in the second period" is equal to the total number of administrations planned during first planned administration of study medication and last planned administration in Maintenance Period, or day of discontinuation, which will be calculated as the duration of Maintenance Period in days ×2. In consideration of whether the first administration is taken in the morning or in the evening, please see Section 10.1.1.

- Overall Period, Treatment compliance (%) will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\sum_{first\ day}^{last\ day}(\text{\# of actual administrations per day})}{\text{total \# of administrations planned during the time the subject was in the study}} \text{ x } 100$$

where "total # of administrations planned during the time the subject was in the study" is equal to the total number of administrations planned during first planned administration of study medication and last planned administration, or day of discontinuation which will be calculated as the duration of exposure to study medication in days ×2. In consideration of whether the first administration is taken in the morning or in the evening, please see Section 10.1.1.

Percent overall compliance for study medication will be summarized for the Evaluation and Maintenance Period in two ways:

- Descriptive statistics will be presented by age category and overall.
- Percent compliance data will be summarized by age category and overall, and will be categorized according to the following categories:
  - < 80%
  - 80 – 120%
  - > 120%.

Summary statistics will be based on the SS_A and SS_M.

7.2 Tables

A table Study Medication Compliance presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics on compliance
- Frequency distribution (<80%, 80-120%, >120%).

7.3 Listings

A subject data listing Study Medication Compliance presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Period
- Formulation (IV or Dry Syrup)
- Number of administrations
- Target number of administrations
- Study Medication Compliance (%)

8 EFFICACY ANALYSES

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be calculated for the continuous secondary efficacy variables and absolute and relative frequencies will be calculated for the categorical efficacy variables.

The primary efficacy variable and potentially the two secondary efficacy variables will be compared with a threshold in a confirmatory way according to the hierarchical testing procedure (see Section 4.5). All efficacy variables which are not tested as confirmatory in the course of the hierarchical testing procedure will be analyzed exploratively only. Descriptive summaries will be created for all these variables irrespective of this.

8.1 Statistical Analysis of the Primary Efficacy Variable

8.1.1 Primary Efficacy Variable for Adjunctive Therapy

First Period

The primary efficacy variable for subjects on adjunctive therapy for the First Period is the percent reduction in partial seizure frequency per week from Baseline to Study Visit 6. In order to include the EEG failures subjects who were enrolled prior to Protocol Amendment 3, analysis visit will be used therefore the primary efficacy variable is presented as the percent reduction in partial seizure frequency per week from Baseline to Analysis Visit 3.

The percent reduction in partial seizures per week from Baseline to Study Visit 6 (Analysis Visit 3) will be calculated as:

$$\frac{\text{Number of partial seizures per week at Baseline} - \text{Number of seizures per week at Analysis Visit 3}}{\text{Number of partial seizures per week at Baseline}} \times 100$$

The number of partial seizures per week at Baseline will be based on the Retrospective Baseline seizure counts (during the 2 weeks prior to Study Visit 1) + Selection Period (Study Visit 1 and Study Visit 2*), see Section 3.3, and will be calculated as:

> [total number of partial seizures entered on the DRC starting at the 2 weeks prior to Study Visit 1 until Study Visit 3 divided by the number of days on which data was entered on the DRC] × 7.

*Study Visit 2 is only applicable for those subjects enrolled prior to Protocol Amendment 3.

The number of seizures per week at Study Visit 6 (Analysis Visit 3) will be based on the seizure count from Analysis Visit 2 to Analysis Visit 3 and will be calculated as:

> [total number of partial seizures entered on the DRC during the period starting 1 day after Study Visit 5 (Analysis Visit 2) through Study Visit 6 (Analysis Visit 3) divided by the number of days, within this period, on which data was entered on the DRC] × 7

Those seizure free days (ie, seizure count is 0 and there is no entry of DRC data) will be included into denominator. Data was NOT entered on DRC only refer to the situation that "Not Done" was ticked on CRF "Seizure Count" page

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the percent reduction in partial seizure frequency per week from Study Visit 6 (Analysis Visit 3) by Baseline age category (3 categories: 1 month to <1 year, 1 year to <2 years, and 2 years to <4 years), and for all subjects combined (overall). The corresponding 95% CI for the median percent reduction at Study Visit 6 (Analysis Visit 3) will be provided by age category and overall. The 95% CI will be derived from a distribution-free method based on order statistics. For example, under the assumption that data does not follow a Gaussian distribution the 95% CI might be calculated by using the UNIVARIATE procedure from SAS® with ciquantdf (alpha=.05) as specification [1]. If the lower limit of the 95% confidence interval for overall is greater than the predefined threshold of 15.0%, the efficacy of LEV is shown significant. If this test shows a significant result, then it will be repeated for the corresponding Study Visit 4 (Analysis Visit 1) and Study Visit 5 (Analysis Visit 2) variable hierarchically (see Section 8.2.1). In that case, the second and the third test is also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed (see Section 4.5).

A summary table based on the FAS_A will be presented:

- Percent Reduction in Partial Seizure Frequency per Week from Baseline to Visit 6 (Analysis Visit 3), by Age Category, Adjunctive Therapy Subjects

Combined First and Second Periods

There is no primary efficacy variable for subjects on adjunctive therapy for the combined First and Second Periods.

8.1.2 Primary Analysis Variable for Monotherapy

There is no primary efficacy variable for subjects on monotherapy.

8.1.3 Sensitivity Analyses of the Primary Efficacy Variable

For the subjects who have important protocol deviations who are considered with impact on efficacy, BLOCF (Baseline Observation Carried Forward) will be applied for the post-baseline value.

A summary table based on the FAS_A will be presented:

- Percent Reduction in Partial Seizure Frequency per Week from Baseline to Visit 6 (Analysis Visit 3), by Age Category, Adjunctive Therapy Subjects, (BLOCF)

8.2 Statistical Analysis of the Secondary Efficacy Variables

8.2.1 Secondary Efficacy Variables for Adjunctive Therapy

First Period:

The secondary efficacy variable for subjects on adjunctive therapy for the First Period is the percent reduction in partial seizure frequency per week from Baseline to Study Visit 4 (Analysis Visit 1) and Study Visit 5 (Analysis Visit 2).

Percent reduction in partial seizure frequency per week from Baseline to Study Visit X will be calculated as:

$$\frac{\text{Number of partial seizures per week at Baseline} - \text{Number of seizures per week at Study Visit X}}{\text{Number of partial seizures per week at Baseline}} \times 100$$

If the analysis of the primary efficacy variable, see Section 8.1.1, shows a significant result (lower limit of the 95% confidence interval for the overall group is greater than the predefined threshold of 15.0%), the lower limit of the 95% CI of the median percent reduction in partial seizure frequency at Study Visit 4 (Analysis Visit 1) and Study Visit 5 (Analysis Visit 2) will also be compared with the predefined threshold of 15.0%.

The following summary tables based on the FAS_A will be presented:

- Percent Reduction in Partial Seizure Frequency per Week from Baseline to Visit 4 (Analysis Visit 1), by Age Category, Adjunctive Therapy Subjects
- Percent Reduction in Partial Seizure Frequency per Week from Baseline to Visit 5 (Analysis Visit 2), by Age Category, Adjunctive Therapy Subjects

Combined First and Second Periods:

The secondary efficacy variables for subjects on adjunctive therapy for the combined First and Second Periods are:

- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline.

  Note: This is combined over the age categories.

- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

  Note: This is combined over the age categories.

Percent reduction in partial seizures per week from Baseline at Analysis Visit X will be calculated as:

$$\frac{\text{Number of partial seizures per week at Baseline} - \text{Number of partial seizures per week at Analysis Visit X}}{\text{Number of partial seizures per week at Baseline}} \text{ x100}$$

The calculation of number of partial seizures per week at Baseline is the same as aforementioned (see Section 8.1.1).

Number of partial seizure frequency per week, as collected on the DRC, is calculated at Analysis Visit x, x=1, 2, 3, 4, …, as:
Number of partial seizures per week at Analysis Visit x = [total number of partial seizures entered on the DRC during the period starting 1 day after Analysis Visit x-1 through Study Day of Analysis Visit x divided by the number of days, within this period, on which data was entered on the DRC] x 7. Those seizure free days (i.e. seizure count is 0 and there is no entry of DRC data) will be included into denominator. Data was NOT entered on DRC only refer to the situation that "Not Done" was ticked on CRF "Seizure Count" page.

The following summary tables based on the FAS_A will be presented:

- Percent Reduction in Seizure Frequency per Week, by Analysis Visit, Adjunctive Therapy Subjects
- Percent Reduction in Seizure Frequency per Week Grouped into 6 Categories by Analysis Visit, Adjunctive Therapy Subjects

8.2.2 Secondary Efficacy Variables for Monotherapy

First Period:

There is no secondary efficacy variable for subjects on monotherapy for the First Period.

Combined First and Second Periods:

The secondary efficacy variables for subjects on monotherapy for the combined First and Second Periods are:

- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline.

Number of partial seizure frequency per week, as collected on the patient dairy form, will be calculated for each Analysis Visit as described in Section 8.2.1 Combined First and Second Periods.

A table Percent Reduction in Seizure Frequency per Week, by Analysis Visit, Monotherapy Subjects presents summary statistics of subjects for each analysis visit on the FAS_M .
Note: This is combined over the age categories.

- For each analysis visit, percent reduction in partial seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined First and Second Periods.

  A table Percent Reduction in Seizure Frequency per Week, Grouped into 6 Categories, by Analysis Visit, Monotherapy Subjects presents the number and percentage of subjects within each of the above defined six categories for all analysis visits on the FAS_M.
  Note: This is combined over the age categories.

8.3 Analysis of Other Efficacy Variables

8.3.1 Derivations of Other Efficacy Variables

The average daily frequency (ADF) of partial seizures as measured by 48h video-EEG will be included as an "other" efficacy variable. Partial seizure count will be based on electrographic seizures with or without clinical correlate depending upon age as specified below. Partial seizures have ILAE seizure code: IA, IB or IC, other seizure codes will not be included in the analysis.

Partial seizure frequency for subjects:

- Aged ≥1 month to ≤6 months will be based on electrographic seizures with an accompanying clinical correlate: item: "Number of electrographic seizures (Partial Onset Seizure only)" and "Number of electro-clinical seizures (Partial Onset Seizure only)" respectively, from Video-EEG CRF. Aged >6 months to <4 years will be based electro-clinical seizures: item "Number of electro-clinical seizures (Partial Onset Seizure only)" from Video-EEG CRF.

The ADF (partial seizures) at Analysis Visit x is defined as:

$$\frac{\#\text{ of partial seizures recorded during the 48 hr video EEG collection period at Analysis Visit x}}{\#\text{ hours of useable video} - \text{EEG time at Analysis Visit x}} \text{ x } 24,$$

where:

- x = -1 (Baseline), 1, or 3; and
- number of hours of useable video-EEG time = total video-EEG time – disconnection time. Total video-EEG time is defined as the difference between the end and the start of recording date and time. Disconnection time is obtained from the "Video-EEG" CRF (item "Total Disconnect Time").

Percent reduction in ADF of partial seizure frequency at Analysis Visit 3 (Study Visit 6) compared to Baseline (Study Visit 2) is defined as:

$$\frac{\text{ADF (partial seizures) at Study Visit 2} - \text{ADF (partial seizures) at Analysis Visit 3 (Study Visit 6)}}{\text{ADF (partial seizures) at Baseline Period}} \times 100$$

where Baseline Period (representing the whole 48 hours video-EEG data collection period) is the visit just before start of administration of study medication (Baseline).

8.3.2 Other Efficacy Variables for Adjunctive therapy/Monotherapy

First Period:

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded prior to Protocol Amendment 3 are:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Analysis Visit 1 (Study Visit 4) and at Analysis Visit 3 (Study Visit 6) compared to Baseline. Percent reduction in ADF of partial seizure frequency will be summarized at Study Visit 4 and Study Visit 6 for all subjects combined.

  A table Percent Reduction in Average Daily Frequency (ADF) of Partial Seizure Frequency at Analysis Visit 1(Study Visit 4) and Analysis Visit 3 (Study Visit 6), Adjunctive Therapy Subjects, presents summary statistics of subjects on adjunctive therapy for Analysis Visit 1 and Analysis Visit 3 on the FAS_A.
  Note: This is combined over the age categories.

  A table Percent Reduction in Average Daily Frequency (ADF) of Partial Seizure Frequency at Analysis Visit 1 (Study Visit 4) and Analysis Visit 3 (Study Visit 6), Monotherapy Subjects, presents summary statistics of subjects on monotherapy for Analysis Visit 1 and Analysis Visit 3 on the FAS_M.
  Note: This is combined over the age categories.

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Analysis Visit 1 (Study Visit 4) and Analysis Visit 3 (Study Visit 6) compared to Baseline.

  A table Percent Reduction in Average Daily Frequency (ADF) of Partial Seizure Frequency Grouped into 6 Categories, Adjunctive Therapy Subjects, presents the number and percentage of subjects, on adjunctive therapy, for Analysis Visit 1 and Analysis Visit 3 within each of the above defined six categories for all analysis visits on the FAS_A.
  Note: This is combined over the age categories.

  A table Percent Reduction in Average Daily Frequency (ADF) of Partial Seizure Frequency Grouped into 6 Categories, Monotherapy Subjects, presents the number and percentage of subjects on monotherapy, for Analysis Visit 1 (Study Visit 4) and Analysis Visit 3 (Study Visit 6), within each of the above defined six categories for all analysis visits on the FAS_M.
  Note: This is combined over the age categories.

Combined First and Second Periods:

The other efficacy variables for the combined First and Second Periods are:

- For each analysis visit, percent reduction in all types of seizure frequency per week from Baseline.

  A table Percent Reduction in All Types of Seizure Frequency per Week during Combined First and Second Periods, Adjunctive Therapy Subjects presents summary statistics of subjects on adjunctive therapy, for each analysis visit on the FAS_A.
  Note: This is combined over the age categories.

  A table Percent Reduction in All Types of Seizure Frequency per Week during Combined First and Second Periods, Monotherapy Subjects presents summary statistics of subjects, on monotherapy, for each analysis visit on the FAS_M.
  Note: This is combined over the age categories.

- For each analysis visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%.
  A table Percent Reduction in All Types of Seizure Frequency per Week Grouped into 6 Categories During Combined First and Second Periods, Adjunctive Therapy Subjects, presents the number and percentage of subjects on adjunctive therapy within each of the above defined six categories for all analysis visits on the FAS_A.
  Note: This is combined over the age categories.

  A table Percent Reduction in All Types of Seizure Frequency per Week Grouped into 6 Categories During Combined First and Second Periods, Monotherapy Subjects, presents the number and percentage of subjects on monotherapy within each of the above defined six categories for all analysis visits on the FAS_M.
  Note: This is combined over the age categories.

The following other efficacy variable is only applicable to Monotherapy:

- Percent of subjects who are continuously 6-months seizure-free monitored by the patient diary.

  A subject is considered 6-months seizure free if they are seizure free for at least 26 x 7 = 182 consecutive days during the combined period of Evaluation Period + Dose adjustment Period + Maintenance Period, otherwise they are not considered seizure free.

  The seizure free time interval must not contain days for which seizure data are missing, ie, "Not done" was checked on the Seizure Count CRF or seizure information is missing otherwise, eg because the complete and required CRF module was not filled out for a certain visit.

  Subjects who received less than 182 days study medication are counted as not having achieved 6-months seizure freedom.

  Missing seizure dates and dates for "not done" rows (in the following both are called "row") are handled as follows:

  – If the row date is missing completely (no entry), two cases can occur

1. The missing row date is the in the first row of the CRF.
   In this case, the visit date of the visit before the documentation visit is imputed.
2. The missing row date is not the first row of the CRF.
   In this case, the date of the day after the last entry in the rows before the row with the missing date is imputed.

– If the row date is missing completely ("UNK", ie, unknown), then the date of the visit before the documentation visit is imputed, independent of the row being the first row or a later one.

– If the year and month of a row date is present but the day is missing, then the same imputation as for a completely missing row date is performed first. If the imputed date is before the first of the month that is documented, then then first day of the month is used.

– If the year of a row date is present but the month is missing, then the same imputation as for a completely missing date is performed first. If the imputed date is before the first of the year that is documented, then then first day of the year is used.

A table Percent and Number of Subjects Who are continuously 6-Months Seizure-Free Monitored by Patient Diary During the Evaluation, Dose-adjustment and Maintenance Period presents the number and percentage of subject on monotherapy who are continuously 6-months seizure-free on the FAS_M.
Note: This is combined over the age categories.

8.4 Listings

A Listing of Partial Seizures Occurrence Recorded on Daily Record Cards presents for subjects in ES for adjunctive therapy:

- Age category
- Site-Subject Number
- Study Visit
- Collection Date
- Number of Partial Seizures

Same listing will be repeated for subjects in ES for monotherapy therapy.

A Listing of Seizures Count by Type of Seizures for subjects in ES for adjunctive therapy:

- Age category
- Site-Subject Number
- Analysis Visit
- Seizure Type (IA, IB, IC, II, III)
- Number of Partial Seizures

Same listing will be repeated for subjects in ES for monotherapy therapy.

A Listing of Partial Seizure Frequency per Week and Percent Reduction of Partial Seizures, as Recorded on Daily Record Cards in FAS_A:

- Age category
- Site-Subject Number
- Retrospective + Selection Period Baseline Value

- Value / Reduction at Visit 4 (Analysis Visit 1)
- Value / Reduction at Visit 5 (Analysis Visit 2)
- Value / Reduction at Visit 6 (Analysis Visit 3)

Same listing will be repeated for subjects in FAS_M.

A Listing of Partial Seizure Frequency per Week and Percent Reduction from Baseline, as Recorded on Daily Record Cards for subjects in FAS_A:

- Age category
- Site-Subject Number
- Analysis Visit Number
- Study Visit
- Baseline Seizure Frequency per Week
- Seizure Frequency per Week at Visit
- Result
- Percent Reduction

Same listing will be repeated for subjects in FAS_M.

The following listings based on the 48h video-EEG will only be applicable to the subjects enrolled prior to Protocol Amendment 3:

A Listing Video EEG Part 1 presents for subjects in FAS_A:

- Age category
- Site-Subject Number
- Study Visit
- Start date/time monitoring
- Stop date/Time monitoring
- Total connect time
- Type of EEG performed
- If other

Same listing will be prepared for subjects in FAS_M.

A Listing Video EEG Part 2 presents for subjects in FAS_A:

- Age category
- Site-Subject Number
- Study Visit
- Was sleep included
- EEG pattern
- Spasms present

Same listing will be prepared for subjects in FAS_M.

A Listing Video EEG Number of Seizures presents for subjects in FAS_A:

- Age category
- Site-Subject Number
- Study Visit

- Non-IS seizures present
- Number of electrographic seizures (Partial Onset Seizure only)
- Number of electro-clinical seizures (Partial Onset Seizure only)
- Number of partial onset seizures (ILAE code I)
- Number of primary generalized seizures (ILAE code II)
- Number of primary generalized seizures (ILAE code II)

Same listing will be prepared for subjects in FAS_M.

A Listing Video EEG Number of Clusters presents for subjects in FAS_A:

- Age category
- Site-Subject Number
- Study Visit
- Non-IS Seizures Present
- Number of Partial Onset Seizures (ILAE code I)
- Number of Generalized Onset Seizures (ILAE code II)
- Number of Unclassified Epileptic Seizures (ILAE code III)

Same listing will be prepared for subjects in FAS_M.

A Listing Average Daily Frequency (ADF) and Percent Reduction of Partial Seizures as Measured by 48 hour Video-EEG presents for subjects in FAS_A:

- Age category
- Site-Subject Number
- Study Visit
- Number of Partial Seizures
- Average Daily Frequency
- Percent Reduction in Average Daily Frequency

Same listing will be prepared for subjects in FAS_M.

A Listing Average Daily Frequency (ADF) and Percent Reduction of Electro-Clinical Partial Seizure Frequency as Measured by 48 hour Video-EEG presents for subjects in FAS_A:

- Age category
- Site-Subject Number
- Study Visit
- Number of Electro-Clinical Partial Seizures
- Average Daily Frequency
- Percent Reduction in Average Daily Frequency

Same listing will be prepared for subjects in FAS_M.

A Listing Average Daily Frequency (ADF) and Percent Reduction of Partial Seizures, as Recorded on Daily Record Cards presents for subjects in FAS_A:

- Age category
- Site-Subject Number

- Analysis Visit number (Week number)
- Result
- Percent reduction

Same listing will be prepared for subjects in FAS_M.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

Results of observed plasma concentrations and dose-normalized LEV plasma concentrations will be presented. Listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

9.1 Pharmacokinetics

9.1.1 Definitions and Derivations

For the calculation of descriptive statistics, a LEV plasma concentration below the lower limit of quantification (LLOQ) will be substituted by LLOQ/2.

Dose-normalized (to 10mg/kg for aged subjects of 6 months and above, or 7mg/kg for age less than 6 months) LEV plasma concentrations are derived as follows:
Dose-normalized LEV plasma concentrations = LEV observed plasma concentration / actual dose given (mg/kg) × 10 (mg/kg) or 7 (mg/kg).

9.1.2 Tables and Figures

Descriptive statistics of LEV observed and dose-normalized plasma concentrations will be summarized per defined time window post-dose by age category (1 month<=Age<6 months, 6 months<=Age<1 year, 1 year<=Age<2 years, 2 years<=Age<4 years) and dose level per administration (10mg/kg, 20mg/kg, 30mg/kg in aged subjects of 6 months and above, 7mg/kg, 14mg/kg, 21mg/kg in aged subjects less than 6 months) in PK-PPS_A and PK-PPS_M. The statistics are calculated only if at least 2/3 of the individual data at a specific sampling point are above or equal to the LLOQ.

Scatter plots of LEV observed plasma concentrations vs. time after last dosing will be presented by age category and dose level. Scatter plots for LEV observed plasma concentrations vs time after last dosing by dose level will be superposed with different symbols in a single graph for each age category.

Scatter plots of LEV observed plasma concentrations vs. time after last dosing will be presented by age category and dose group. Scatter plots for LEV observed plasma concentrations vs time post dose by dose group will be superposed with different symbols in a single graph for each dose group. The dose groups are defined as:

- low dose group, 7mg/kg in aged subjects less than 6 months and 10mg/kg in aged subjects of 6 months and above;
- middle dose group, 14mg/kg in aged subjects less than 6 months and 20mg/kg in aged subjects of 6 months and above;

- high dose group, 21mg/kg in aged subjects less than 6 months and 30mg/kg in aged subjects of 6 months and above

Scatter plots of LEV dose-normalized plasma concentrations vs. time after last dosing will be presented by age category and dose level. Scatter plots for LEV dose-normalized plasma concentrations vs time after last dosing by dose level will be superposed with different symbols in a single graph for each age category.

Another scatter plot for LEV dose-normalized plasma concentrations vs time after last dosing will be presented by age category and AED category with different symbols in a single graph.

Scatter plots for LEV dose-normalized plasma concentrations vs time post dose by age category will be superposed with a scatter plot for LEV dose-normalized plasma concentrations vs time pose dose in N01223 with different symbols in a single graph. Dose-normalization of LEV plasma concentrations in N01223 will be performed to 10mg/kg for a subject with a body weight less than 50kg and to 500mg for a subject with a body weight more than or equal to 50kg.

In addition, scatter plots for LEV dose-normalized plasma concentrations vs time pose dose will be superposed with simulated LEV plasma concentration-time profiles based on the population PK model established in N01288 by age category. The data of LEV plasma concentrations and times in N01223 and N01288 are provided from data management group in UCB.

9.1.3 Listings

A subject data listing LEV Plasma Concentration Monitoring will present for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Treatment Group
- Region/Country/Site-Subject Number
- Gender/Age(years)/ Weight(kg)
- Visit
- Not Done (with a flag 'N')
- Last Study Medication prior to Blood Sampling Datetime (YYYY-MM-DDThh:mm)/ Relative Day
- Blood Sampling Date time (YYYY-MM-DDThh:mm:ss)/Relative Hours to Last Medication
- Last Dosage (mg/intake)
- Plasma LEV Concentration (µg/ml)
- Time Window [-0 (Just before dosing), >0-1, >1-2, >2-4, >4-8, >8-12, and >12 hours post dosing]

- Dose Normalized Plasma Level (µg/ml): equivalent to 10mg/kg/administration for aged subjects of 6 months and above or 7mg/kg/administration for aged subjects less than 6 months

9.2 Pharmacodynamics

Not applicable.

10 SAFETY ANALYSES

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

Summaries will be presented for: AEs, ECG data, vital signs and weight (continuous) data, and PCS data.

Safety data will be summarized for the Safety Sets, see Section 3.5.2.

10.1 Extent of Exposure

The duration of exposure to LEV, as defined in Section 3.2.7, will be summarized as a continuous parameter (in days). Descriptive statistics for the duration of exposure to study medication in days will be presented by age category and overall. Handling of missing study medication data is described in Section 4.2.4.

The following listings will be provided: study medication administration and exposure to study medication.

10.1.1 Definitions and Derivations

Duration in days of exposure to study medication is calculated as:

Start date = Date of first administration of study medication

End date = Date of last administration of study medication

A) Start Date (Morning) and End Date (Evening) then Duration=End date - Start date + 1

B) Start Date (Morning) and End Date (Morning) then Duration=End date - Start date + 0.5

C) Start Date (Evening) and End Date (Evening) then Duration=End date - Start date + 0.5

D) Start Date (Evening) and End Date (Morning) then Duration=End date - Start date.

Note: The date of the first and last administration of study medication is recorded on the "First Administration" and the "Study Termination" eCRFs, respectively.

Note: Missing values for date of last administration of study medication are imputed as specified in Section 4.2.4.

The exposure duration in days for a period is assumed to be equal to the duration of the respective period except for the Down-titration Period. For the Down-titration Period the exposure duration is calculated as:

Date of last administration of study medication – Date of first day of period +1.

If date of last administration of study medication is missing, the last complete administration date will be used.

For start and end dates of periods see Section 2.3.1 and Section 5.1.1.4 .

Details on study medication administration are recorded on the "Study Medication Administration – IV" and "Study Medication Administration – Dry Syrup" eCRFs.

The modal dose is calculated using the daily dose (morning dose + evening dose). If there are tied cases, the later dose will be the modal dose.

10.1.2 Tables

A table Study Medication Duration presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics on study medication duration

A table Study Medication Administration presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics on mean daily dose and modal dose of study medication

10.1.3 Listings

A subject data listing Exposure to Study Medication presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Period
- Date of First Dose
- Date of Last Dose
- Study Medication Duration (days)
- Mean daily dose

10.2 Adverse Events

An overview of AEs presents number and percent of subjects with any TEAE, serious TEAEs, TEAEs leading to discontinuation, TEAEs requiring dose change, any drug-related TEAEs, severe TEAEs, as well as deaths together with the number of individual occurrences in those categories.

Incidences of TEAEs by SOC and PT are presented together with the number of individual occurrences for , TEAEs, , serious TEAEs and serious drug-related TEAEs, and TEAEs leading to discontinuation of study drug.

Additional tables are presented for TEAEs by intensity and for a subset of TEAEs occurring in at least 5% of subjects.

Secondary safety variables for the First Period are: Incidence of TEAEs, Incidence of SAEs, and Incidence of TEAEs leading to discontinuation

Secondary safety variables for the combined First and Second Periods are: Incidence of TEAEs during the combined First and Second Periods, Incidence of SAEs during the combined First and Second Periods, and Incidence of TEAEs leading to discontinuation during the combined First and Second Periods.

Presentations are done for subjects on adjunctive therapy and for subjects on monotherapy, separately.

Subject data listings also cover the verbatim term and further details like start and end date, if applicable.

10.2.1 Definitions and Derivations

The treatment-emergent adverse events (TEAEs) are defined as those events that started on or after the date (and time) of first dose of study medication, or adverse events whose intensity worsened on or after the date (and time) of first dose of study medication.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

10.2.1.1 Categorization of AEs

Adverse events are categorized as pre-treatment and treatment-emergent:

- Pre-treatment: Onset date before first dose of study medication
- Treatment-emergent: Onset date (including severity-worsening) on or after first dose of study medication

10.2.1.2 Assignment of AEs to Periods/Onset of AEs

An AE is assigned to that study period the subject is in during onset of the AE. For the definitions of study periods see Section 2.3.1.

10.2.1.3 AEs Leading to Discontinuation

AEs leading to discontinuation are identified using information documented on the AE CRF.

Both of the following needs to be documented for an event being classified as leading to discontinuation:

- Item “Action Taken with Study Medication” is specified as “Drug permanently withdrawn”
- Item “Did Adverse Event Lead to Dropout?” is specified with “Yes”

10.2.1.4 Drug related AE

A drug-related TEAE is defined as any TEAE with ”Relationship to Study Medication” recorded as “related” on the CRF as assessed by the investigator or with missing assessment of the causal relationship.

10.2.1.5 Dose at AE Onset

As a conservative approach, in case an AE has onset date on a day with 2 different total daily doses, the lower dose is used.

10.2.1.6 Incomplete Dates

Data handling rules for management of missing or partial start or stop dates for adverse events should follow those defined in the Section 4.2.3.

10.2.2 Tables

Tables will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

AE Summaries

For the First Period all TEAE summaries will be presented for all age categories combined on the SS_A and SS_M.

For the combined First and Second Period all TEAE summaries will be presented for all age categories combined on the SS_A and SS_M.

The following summaries will be produced, for the First, and for the combined First and Second Periods):

- Number and percent of subjects with AEs – Overview:
  Overview of the Incidence of AEs will include all subjects with at least one TEAE, serious TEAEs, subject discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs, and all deaths (AEs leading to death).
- Incidence of AEs – Overview
- Number and percent of subjects with TEAEs, and Incidence of TEAEs
- Number and percent of subjects with serious TEAEs, and Incidence of serious TEAEs
- Number and percent of subjects with TEAEs by relationship to study medication, and Incidence of TEAEs by relationship to study medication
- Number and percent of subjects with serious TEAEs by relationship to study medication, and Incidence of serious TEAEs by relationship to study medication
- Number and percent of subjects with serious drug-related TEAE
- Number and percent of subjects with TEAEs by Intensity, and Incidence of TEAEs by Intensity
- Number and percent of subjects with serious TEAEs occurring in at least 5% of the subjects, and Incidence of serious TEAEs occurring in at least 5% of the subjects
- Number and percent of subjects with TEAEs leading to (permanent) discontinuation of study medication
  Note: permanent discontinuation: when in the Adverse Event CRF the item “Action taken with study Medication” is answered with “Drug Permanently Withdrawn”. And Incidence of TEAEs leading to (permanent) discontinuation of study medication

AEs will be summarized by MedDRA SOC and MedDRA PT. The number and percentage of subjects experiencing each event at least once will be summarized.

10.2.3 Listings

A listing TEAE Glossary represents the mapping of reported terms to preferred terms and system organ class based on the MedDRA coding dictionary:

- System Organ Class
- Preferred Term
- Reported Term

A subject data listing All Adverse Events presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Region/Country/Site/Subject Number
- Gender/Age/Race/Weight
- System Organ Class/Preferred Term/Reported Term
- AE Onset Date (Relative Day)/AE Outcome Date (Relative Day)/Period
- AE Duration/Dose at Onset/Days on Dose at Onset/Total Days on Treatment
- Seriousness/Intensity
- Pattern of Event
- AE Led to Dropout?
- Relationship to Study Medication/Action Taken with Study Medication/Other Action Taken / AE Outcome

The listing is repeated for:

- Treatment Emergent AEs Leading to Discontinuation
- Deaths and Other Serious TEAEs

10.3 Clinical Laboratory Evaluations

All laboratory data summaries will be presented by analysis visit.

Shifts from baseline to end of treatment based on the normal range (ie, low, normal, high, and missing) for each hematology and clinical chemistry lab parameter will be presented.

The number and percentage of subjects with possibly clinically significant treatment-emergent laboratory values (hematology and clinical chemistry) as defined in Section 12.3.1 and Section 12.3.2, respectively, will be summarized. Possibly clinically significant treatment-emergent laboratory values are those that are observed during the defined treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period. A

subject number table will be presented for subjects with laboratory assessments meeting the marked abnormality criteria.

Individual subject data listings present laboratory data including change from Baseline and flags for abnormal and PCS values.

Subjects who meet one or more of the criteria presented in Appendix 12.3.3 for potential drug-induced liver injury (PDILI) at any time-point (from both scheduled and unscheduled visits) will be listed. The listing will display only visits for which at least one of the above criteria was fulfilled for a given subject, and will display all results obtained at that visit for the specified variables. Potential Hy's law cases will be flagged. If applicable, a summary of subjects who met the criteria for PDILI will be presented separately from all relevant data collected.

PDILI laboratory results and additional PDILI information will be listed. If specific PDILI information collected separately is matching to the entries in the standard eCRF pages collected for all subjects, the specific PDILI information will be added to the corresponding listing for the standard eCRF information (eg, lifestyle information is collected for all study subjects, the additional PDILI information for alcohol and illicit drug use will be included in the listings for lifestyle). For information collected on top (eg, family history of PDILI) a new listing will be generated.

10.3.1 Definitions and Derivations

For continuous laboratory variables (hematology and clinical chemistry) summary statistics of actual values and change from Baseline values will be presented.

In tables that are provided by period, percentages are based on the number of subjects who are at risk for a certain period per age category in the respective analysis set. Subjects who entered a period are regarded as "at risk" for this period.

The list of laboratory variables is given in Section 12.1.

10.3.1.1 Blood Sample

Blood samples are analyzed by a central laboratory and data are available electronically including SI units as well as an assessment of abnormality based on normal ranges (eg, high, low; adjusted for age and gender where applicable).

Change from Baseline (see Section 3.3) is calculated for each post Baseline visit according to the visit schedule including unscheduled visits and for the Last Visit.

A variable representing categories for possibly clinically significant treatment-emergent (PCST) abnormal values is created for selected hematology and blood chemistry parameters (Table 12–1 and Table 12–2):

- Too low
- Not PCS
- Too high

PCST abnormal values are defined as any treatment emergent laboratory values meeting the criteria (UCB 2012, GUIDANCE DOCUMENT, Clinical and Laboratory Possibly Clinically Significant Treatment Emergent (PCST) Criteria For Clinical Development Programs in TA CNS).

10.3.1.2 Ordering of Laboratory Parameters

The tables and listings, parameters are presented in the following order (Section 12.1):

- Hematology
  Quantitative data: Red Blood Cell (RBC, also called erythrocytes) count, hemoglobin, hematocrit, platelets, White Blood Cell (WBC, also called leukocytes) count, differential blood count, (basophil, eosinophil, neutrophil, lymphocyte, monocyte), reticulocyte count, MCV, MCH, and MCHC
- Blood chemistry
  Quantitative data: AST, ALT, GGT, ALP, Total bilirubin, Creatinine, Creatinine clearance, Sodium, Potassium, Calcium, Total protein, and Albumin, BUN,

10.3.2 Tables

A table Hematology Observed Values and Changes from Baseline presents for subjects on adjunctive therapy and for subjects on monotherapy, separately per analysis visit summary statistics:

- For absolute values
- For Change from Baseline values.

This by visit presentation includes scheduled visits and Last Visit.

The table is repeated for:

- Blood Chemistry Observed Values and Changes from Baseline values.

A table Hematology: Shift from Baseline to End of Treatment presents for subjects on adjunctive therapy and for subjects on monotherapy, separately the number of shifts from:

- “Low” at Baseline and “Low” at End of Treatment
- “Low” at Baseline and “Normal” at End of Treatment
- “Low” at Baseline to “High” at End of Treatment
- “Normal” at Baseline to “Low” at End of Treatment
- “Normal” at Baseline to “Normal” at End of Treatment
- “Normal” at Baseline to “High” at End of Treatment
- “High” at Baseline to “High” at End of Treatment
- “High” at Baseline to “Normal” at End of Treatment
- “High” at Baseline to “Low” at End of Treatment

The table is repeated for:

- Blood Chemistry.

A table Treatment-emergent PCS Hematology by Analysis Visit presents the number and percentage of subjects with treatment-emergent PCS criteria (Too low, Too high) for each of the respective parameters. Tables will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

Note: Category "Not PCS" is omitted due to limited usefulness.

Frequencies are presented as:

- n over Nobs with n being the number of subjects with PCS criterion for the respective variable at least at one visit during that period and Nobs being the number of subjects with at least 1 non-missing measurement for respective variable during that period.
- Percentage (%) based on Nobs

The table is repeated for:

- Blood Chemistry PCS Data.

A table Hematology PCS Shift from Baseline presents, for each period and for the combined periods changes from Baseline in the PCS abnormality category at any time during the respective period and overall. Tables will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

The table presents the following settings:

- "Too low" at Baseline and "Too low" at least at one visit during that period
- Shifts from "Too low" at Baseline to "Too high" at least at one visit during that period
- Shifts from "Not PCS" at Baseline to "Too low" at least at one visit during that period
- Shifts from "Not PCS" at Baseline to "Too high" at least at one visit during that period
- "Too high" at Baseline and "Too high" at least at one visit during that period
- Shifts from "Too high" at Baseline to "Too low" at least at one visit during that period
- "Too low", "Not PCS", and "Too high" at Baseline for those subjects having at least one measurement during that period.

Note: Shifts to status "No PCS" are omitted due to limited usefulness.

Frequencies are presented as:

- n over Nobs with n being the number of subjects with at least one measurement during that period meeting the criteria for the respective variable and Nobs being the number of subjects with at least one non-missing measurement for the respective variable during that period and at baseline.

- Percentage (%) based on Nobs

For this table a subject can appear in more than one shift.

The table is repeated for:

- Blood Chemistry PCS Shifts.

A table Potential Drug Induced Liver Injury (PDILI) Data presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, the number and percentage of subjects with the following criteria:

- ALT or AST ≥ 5xULN
- ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

Frequencies are presented as:

- n over Nobs with n being the number of subjects with at least one measurement during that period meeting the criteria for the respective variable and Nobs being the number of subjects with at least one non-missing measurement for the respective variable during that period and at baseline.
- Percentage (%) based on Nobs

10.3.3 Listings

A subject data listing Hematology Laboratory Results presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Region/Country/Site/Subject Number
- Gender/Age/Race/Weight
- Laboratory Function Panel
- Variable
- Normal Range
- Analysis Visit
- Lab Not Done
- Date Sample Taken/Relative Day
- Fasting?
- Result / Flag
- Change from Baseline / Flag
- Abnormal

The column “Abnormal” represents the PCS criterion that is met, if applicable.

The subject data listing is repeated for:

- Blood Chemistry Laboratory Values.

A listing of Subjects with Potential Drug-Induced Liver Injury presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Region/Country/Site/Subject Number
- Gender/Age/Weight
- Analysis Visit
- ALT value
- AST value
- Bilirubin value

Note: Potential Drug-Induced Liver Injury criteria presented are:
(ALT >3 x ULN or AST >3 x ULN) and Bilirubin >2 x ULN, and
(ALT >5 x ULN or AST >5 x ULN), where ULN=Upper Limit of Normal Range

10.4 Vital signs, Physical Findings, and Other Observations Related to Safety

10.4.1 Vital Signs

PCST abnormal vital sign values are any treatment emergent parameters meeting the criteria as described in the UCB guidance document.

For each scheduled post-Baseline visit and for Last Visit descriptive statistics for observed values and change from Baseline values are presented for each vital sign parameter. In addition, number and percent of subjects with PCS values are presented by visit and by period for vital sign parameters. In addition, a table presents per period and overall changes from Baseline in the PCS category.

Individual subject data listings present vital sign data including change from Baseline and flags for PCS values.

10.4.1.1 Definitions and Derivations

Vital signs parameters are documented in the Vital signs CRF.

Change from Baseline (CfB) is calculated for each post Baseline visit according to the visit schedule including unscheduled visits and for Last Visit:

CfB= Post-baseline value – Baseline value.

The vital signs abnormality criteria are defined as presented in Section 12.5.

A variable representing categories for possibly clinically significant treatment-emergent (PCST) abnormal values is created for vital sign parameters pulse rate, systolic blood pressure, diastolic blood pressure, and temperature:

- Too low
- Not PCS
- Too high

PCST abnormal values are any treatment emergent vital sign values meeting the criteria (UCB 2012, GUIDANCE DOCUMENT, Clinical and Laboratory Possibly Clinically Significant Treatment Emergent Criteria (PCST) Criteria for Clinical Development Programs in TA CNS).

In tables that are provided by period, percentages are based on the number of subjects who are at risk for a certain period per age category in the respective analysis set. Subjects who entered a period are regarded as "at risk" for this period.

10.4.1.2 Tables

A table Vital Signs Observed Values and Changes from Baseline presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, per analysis visit summary statistics:

- For observed values (systolic blood pressure, diastolic blood pressure, pulse rate)
- For Change from Baseline in vital sign parameters.

This by analysis visit presentation includes scheduled visits and Last Visit.

A table Post-baseline PCS Vital Signs by Analysis Visit presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, per analysis visit and overall the number and percentage of subjects with PCS criteria (Too low, Too high) for each of the following parameters:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Temperature

Note: Category "Not PCS" is omitted due to limited usefulness.

Frequencies are presented as

- n over Nobs with n being the number of subjects with PCS criterion for the respective variable at least at one visit and Nobs being the number of subjects with at least one non-missing measurement.
- Percentage (%) based on Nobs.

10.4.1.3 Listings

A subject data listing Vital Signs presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Region/Country/Site/Subject Number
- Gender/Age/Race/Weight
- Vital sign variable
- Analysis Visit
- Date/Relative Day
- Result
- Change from Baseline
- Abnormal

The column "Abnormal" represents the PCS category, if applicable.

10.4.2 Electrocardiograms

A summary of ECG data will be presented by visit. A frequency distribution on the abnormality status of the ECG assessment is presented by visit. In addition, a table presents changes from Baseline in the abnormality assessment of ECG.

10.4.2.1 Definitions and Derivations

The overall result of the ECG is documented in the 12-Lead ECG Interpretation CRF as:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant.

No individual ECG parameter is documented in the CRF or is available for data analysis

10.4.2.2 Tables

A table 12-lead ECG Report by Analysis Visit presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, for each analysis visit the frequency distribution on the abnormality status of the ECG assessment:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

Frequencies are presented as:

- n over Nobs with n being the number of subjects with an assessment in that category at that visit and Nobs being the number of subjects with a non-missing ECG report at that visit

- Percentage (%) based on Nobs

A table 12-lead ECG Shifts from Baseline by Analysis Visit presents for each analysis visit changes in the abnormality assessment from baseline:

The table presents the following settings:

- "Normal" at Baseline and at the respective post-baseline visit
- Shifts from "Normal" to "Abnormal, not clinically significant" or "Abnormal, clinically significant"
- "Abnormal, not clinically significant" at Baseline and at the respective post-baseline visit
- Shifts from "Abnormal, not clinically significant" to "Normal" or "Abnormal, clinically significant"
- "Abnormal, clinically significant" at Baseline and at the respective post-baseline visit
- Shifts from "Abnormal, clinically significant" to "Normal" or "Abnormal, not clinically significant"

Frequencies are presented as:

- n over Nobs with n being the number of subjects with an assessment in that category and Nobs being the number of subjects with a non-missing ECG report at baseline and that visit
- Percentage (%) based on Nobs

10.4.2.3 Listings

The subject data listing 12-Lead ECG Findings presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Region/Country/Site/Subject Number
- Gender/Age/Race/Weight
- Analysis Visit
- ECG Date and Time/Relative Day
- ECG evaluated by (investigator/cardiologist)
- Finding
- Abnormal Result

The column "Abnormal results" represents the pre-defined categorization given in the respective ECG CRF and only abnormal findings are listed.

10.4.3 Body Weight and Height

A summary of body weight and height data, including change from baseline data, will be presented by visit. A frequency distribution on the abnormality status of the weight data will be presented by visit.

10.4.3.1 Definitions and Derivations

A variable representing categories for PCST abnormal values is created for body weight:

- Too low
- Not PCS
- Too high

(see Table 12–3, Table 12–4 and Table 12–5)

In tables that are provided by period, percentages are based on the number of subjects who are at risk for a certain period per age category in the respective analysis set. Subjects who entered a period are regarded as "at risk" for this period.

10.4.3.2 Tables

A table Weight and Height presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Summary statistics on weight and height by visit
- Summary statistics on change from baseline on weight and height by post-baseline visit

Missing is presented as category only if this is applicable for a certain variable.

A table Post-baseline PCS Weight by Analysis Visit presents for subjects on adjunctive therapy and for subjects on monotherapy, separately, per analysis visit the number and percentage of subjects with PCS criteria (Too low, Not PCS, Too high) for the following parameter:

- Body Weight

10.4.3.3 Listings

A subject data listing Weight and Height presents for subjects on adjunctive therapy and for subjects on monotherapy, separately:

- Age Category
- Site/Subject Number
- Analysis Visit
- Date and Relative Day
- Height
- Weight
- Abnormal (weight)

10.4.4 Concomitant Medical Procedures

Concomitant medical procedures will be listed.

10.4.4.1 Definitions and Derivations

Not applicable.

10.4.4.2 Tables

None.

10.4.4.3 Listings

Procedure names are not coded, therefore only a listing is presented.

A listing Concomitant Medical Procedures presents for subjects on adjunctive therapy and for subjects on monotherapy, separately for each concomitant medical procedure:

- Age Category
- Site/Subject Number
- Date of Procedure/Relative Day
- Procedure (Reported Term)
- Procedure related to (Epilepsy, Lack of Efficacy, Adverse Event, Elective Procedure, Other)

10.4.5 Assessment of Suicidality

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

10.4.5.1 Definitions and Derivations

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This will be completed according to the protocol schedule of study assessments. The C-SSRS is not validated and will not be used for subjects <6 years of age.

10.4.5.2 Tables

Not applicable.

10.4.5.3 Listings

Data as recorded on the "C-SSRS (Since Last Visit)" will be presented by subject number.

A listing C-SSRS Suicidality presents for subjects on adjunctive therapy and for subjects on monotherapy, separately the following:

- Age Category
- Site/Subject Number
- Visit
- Assessment Date/Relative Day
- Module
- Time point
- Question
- Response

11 REFERENCES

[1] Hahn G.J. and Meeker W.Q., Statistical Intervals: A Guide for Practitioners, 1991, New York: John Wiley & Son

[2] GUIDANCE DOCUMENT, Clinical and Laboratory Possibly Clinically Significant Treatment Emergent Criteria (PCST) Criteria For Clinical Development Programs in TA CNS (UCB 14JUN2012)

12 APPENDICES

12.1 Order of Laboratory Variables in Tables and Listings

For tables and listings the order for hematology variables is:

1. Red blood cell count (also called erythrocytes)
2. Hemoglobin
3. Hematocrit
4. Platelet count
5. White blood cell count (also called leukocytes)
6. Basophil count
7. Basophils/Leukocytes (%)
8. Eosinophil count
9. Eosinophils/Leukocytes (%)
10. Neutrophil count
11. Neutrophils/Leukocytes (%)
12. Lymphocyte count
13. Lymphocytes/Leukocytes (%)
14. Monocyte count
15. Monocytes/Leukocytes (%)
16. Reticulocyte count
17. Mean Corpuscular Volume (MCV)
18. Mean Corpuscular Hemoglobin (MCH)
19. Mean Corpuscular HGB Concentration (MCHC)

For tables and listings the order for blood chemistry variables is:

1. Aspartate Aminotransferase (AST)
2. Alanine Aminotransferase (ALT)
3. Gamma Glutamyl Transferase (GGT)
4. Alkaline Phosphatase (ALP)
5. Total Bilirubin
6. Creatinine
7. Creatinine Clearance
8. Sodium
9. Potassium

10. Calcium
11. Total Protein
12. Albumin
13. Blood Urea Nitrogen (BUN)

12.2 Listing of AEDs

The following is a list of antiepileptic drugs (generic name):

- Acetazolamide
- Acetylpheneturide
- Amino (diphenylhydantoin) valeric acid
- Barbexaclone
- Beclamide
- Brivaracetam
- Carbamazepine
- Carisbamate
- Clobazam
- Clonazepam
- Diclofenamide
- Eslicarbazepine
- Ethadione
- Ethosuximide
- Ethotoin
- Felbamate
- Fosphenytoin
- Gabapentin
- Ilepcimide
- Lacosamide
- Lamotrigine
- Levetiracetam
- Mesuximide
- Metharbital
- Methylphenobarbital
- Mephenytoin
- Nitrazepam
- Oxcarbazepine
- Paramethadione
- Perampanel

- Phenacemide
- Pheneturide
- Phenobarbital
- Phensuximide
- Phenytoin
- Pregabalin
- Primidone
- Progabide
- Retigabine
- Rufinamide
- Stiripentol
- Sultiame
- Tiagabine
- Topiramate
- Trimethadione
- Valproic acid
- Valpromide
- Vigabatrin
- Zonisamide

Note: An AED that contains more than one compound in this list is not counted as 1 AED.

The number of compounds contained in 1 AED is counted as the number of AED administered.

It is prohibited that subjects take levetiracetam other than IMP during the study. Antiepileptic drugs that have not been approved in Japan are prohibited.

12.3 Possibly Clinically Significant Treatment-Emergent Laboratory Values

The following two tables are obtained from [2].

12.3.1 Hematology

Table 12–1: PCST values for Hematology

Parameter	Age range	Unit (conventional)	Abnormality Criteria (conventional)	Unit	Abnormality Criteria (standard)
Red blood cell count	<2 years	10^{12}/L	< 3.0	T/L	< 3.0
	≥2 years		< 3.5		< 3.5
Hematocrit	<2 years	%	≤ 27	%	≤ 27
			> 45		> 45
	≥2 y - <18 y		≤ 29		≤ 29
			> 47		> 47
Hemoglobin	<2 years	g/dL	≤ 9.0 > 15.0	g/L	≤ 90 > 150
	≥2 y – <18 y		≤ 9.5 > 16.0		≤ 95 > 160
Platelets	>1 month	10^9/L	≤ 100	G/L	≤ 100
			> 600		> 600
White blood cell count	<12 years	10^9/L	< 3.5	G/L	< 3.5
			> 15.0		> 15.0
Neutrophil count	>1 month	10^9/L	< 1.5	G/L	< 1.5
Lymphocyte	<6 months	%	≤ 30.0	%	≤ 30.0
	6 m - <6 y		≤ 22.0		≤ 22.0
Monocyte	>1 month	%	≥ 20.0	%	≥ 20.0
Eosinophil	>1 month	%	≥ 10.0	%	≥ 10.0
Basophil	>1 month	%	≥ 3.0	%	≥ 3.0
Reticulocyte			$		$
MCV			$		$
MCH			$		$
MCHC			$		$

Abbreviations: dL = deciliter; L = liter; m: month; mg = milligram; mmol = millimoles; µmol = micromoles; U = unit; y: year
MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume
[$] Not presented in reference [2]

Note: The adjusted age (Section 3.2.5.2) at the assessment/visit will be used to determine within which percentile the subject is included.

12.3.2 Chemistry

Table 12–2: PCST values for Chemistry

Parameter	Age range	Unit (conventional)	Abnormality Criteria (conventional)	Unit	Abnormality Criteria (standard)
AST	<14 years	U/L	> 180	U/L	> 180
ALT	<1 year	U/L	$	U/L	$
	1 yr - <18 y		> 90		> 90
GGT	<6 month	U/L	> 522	U/L	> 522
	6 m - <1 y		> 279		> 279
	1 y - < 13 y		> 66		> 66
Alkaline Phosphatase	<4 year	U/L	> 690	U/L	> 690
	4 y - <10 y		> 834		> 834
Total Bilirubin	> 1 month	mg/dl	≥ 1.5	µmol/L	≥ 25.656
BUN	<1 year	mg/dl	> 21	mmol/L	> 7.497
	≥1 year		> 30		> 10.71
Creatinine	<1 year	mg/dL	$	µmol/L	$
	1 y - <10 y		> 0.9		> 79.56
Creatinine Clearance [#]	All	ml/min	< 70	mL/s	< 1.169
Sodium	> 1 month	mEq/L	≤ 130	mmol/L	≤ 130
			≥ 150		≥ 150
Potassium	< 1 year	mEq/L	< 3.0	mEq/L	< 3.0
			> 6.5		> 6.5
	≥ 1 year		< 3.0		< 3.0
			> 5.8		> 5.8
Calcium	< 1 year	mg/dL	< 6.9	mmol/L	< 1.725
			> 12.2		> 3.05
	1 y - <18 y		< 7.4		< 1.85
			> 11.7		> 2.925
Total Protein	<2 months	g/dL	$	g/L	$
	2 m - <1 yr		< 3.0		< 30
			> 10.0		> 100
	≥1 year		< 4.3		< 43
			> 10.0		> 100
Albumin	<1 year	g/dL	< 1.6	g/L	< 16
			> 6.0		> 60
	≥1 year		< 2.4		< 24
			> 7.0		> 70

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; GGT: gamma-glutamyl transferase; BUN = blood urea nitrogen; dL = deciliter; L = liter; mg = milligram; mmol = millimoles; µmol = micromoles; U = unit; m=month (a month is defined as 30 days); y = years (a year is defined as 365.25 days)

[$] Not presented in reference [2]

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

Note: The adjusted age (Section 3.2.5.2) at the assessment/visit will be used to determine within which percentile the subject is included.

12.3.3 Required Investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 11.2.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Hepatology consult if there is no evidence of resolution (see Follow up requirements).[c] Discussion with Medical Monitor required.	IMP discontinuation required if any of the following occur: Subject cannot comply with monitoring schedule. Liver chemistry values continue to increase during 2 week monitoring period. Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 2 week monitoring period.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.2.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: Discontinue IMP if levels remain ≥5xULN (and ≥2x baseline); monitor until values normalize, stabilize, or return to within baseline values.[d] Continue IMP if levels are no longer ≥5xULN (and ≥2x baseline); continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.3.4 PDILI Laboratory Measurements

Virology-related	Hepatitis E IgM antibody
	HBsAg
	Hepatitis A IgA antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophil antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgA=immunoglobulin A; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

12.4 PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

12.5 Vital Signs Abnormality Criteria

Table 12–3: Vital Signs Abnormality Criteria

Parameter	Age Range	Abnormality Criteria
Pulse Rate (beats/minute)	<6 months	< 100 bpm > 180 bpm
	6 months - <3 years	< 90 bpm > 150 bpm
	3 years to <12 years	< 60 bpm > 130 bpm
Systolic Blood Pressure (mmHg)	<6 months	< 60 mmHg > 100 mmHg
	6 months - <3 years	< 70 mmHg > 120 mmHg
	3 years to <12 years	< 80 mmHg > 140 mmHg
Diastolic Blood Pressure (mmHg)	<6 months	< 40 mmHg > 65 mmHg
	6 months - <3 years	< 45 mmHg > 75 mmHg
	3 years to < 12 years	< 50 mmHg > 80 mmHg
Temperature	>1 month	>101 ºF (38.3 ºC)
Body Weight	1 month - <17 years	<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]

[a] For centiles see Table 12–4 and Table 12–5
A month is defined as 30 days; a year is defined as 365.25 days.
Data obtained from: GUIDANCE DOCUMENT, Clinical and Laboratory Possibly Clinically Significant Treatment Emergent Criteria (PCST) Criteria For Clinical Development Programs in TA CNS (UCB 14JUN2012)

Note: The adjusted age (Section 3.2.5.2) at the assessment/visit will be used to determine within which percentile the subject is included.

12.6 Body Weight Values

Table 12–4: Body Weight Values (kg) by Age in Months/Years and Months for Males

Age	Percentile						
	3	10	25	50	75	90	97
6 to <7 months	6.44	6.94	7.44	8.00	8.56	9.07	9.57
7 to <8 months	6.73	7.21	7.71	8.27	8.84	9.36	9.87
8 to <9 months	6.96	7.44	7.94	8.50	9.08	9.61	10.14
9 to <10 months	7.16	7.64	8.13	8.70	9.29	9.83	10.37
10 to <11 months	7.34	7.81	8.31	8.88	9.48	10.03	10.59
11 to <12 months	7.51	7.98	8.48	9.06	9.67	10.23	10.82
1 yr and 0 to <1 month	7.68	8.15	8.65	9.24	9.86	10.44	11.04
1 yr and 1 to <2 months	7.85	8.32	8.83	9.42	10.05	10.65	11.28
1 yr and 2 to <3 months	8.02	8.49	9.00	9.60	10.25	10.86	11.51
1 yr and 3 to <4 months	8.19	8.67	9.18	9.79	10.44	11.08	11.75
1 yr and 4 to <5 months	8.36	8.84	9.35	9.97	10.64	11.29	11.98
1 yr and 5 to <6 months	8.53	9.01	9.53	10.16	10.84	11.51	12.23
1 yr and 6 to <7 months	8.70	9.18	9.71	10.35	11.04	11.73	12.47
1 yr and 7 to <8 months	8.86	9.35	9.89	10.53	11.25	11.95	12.71
1 yr and 8 to <9 months	9.03	9.52	10.06	10.72	11.45	12.17	12.96
1 yr and 9 to <10 months	9.19	9.69	10.24	10.91	11.65	12.39	13.20
1 yr and 10 to <11 months	9.36	9.86	10.41	11.09	11.85	12.61	13.45
1 yr and 11 to <12 months	9.52	10.03	10.59	11.28	12.06	12.83	13.69
2 yrs and 0 to <6 months	10.06	10.60	11.19	11.93	12.76	13.61	14.55
2 yrs and 6 to <12 months	10.94	11.51	12.17	12.99	13.93	14.90	16.01
3 yrs and 0 to <6 months	11.72	12.35	13.07	13.99	15.04	16.15	17.43
3 yrs and 6 to <12 months	12.42	13.10	13.89	14.90	16.08	17.34	18.82
4 yrs and 0 to <6 months	13.07	13.80	14.65	15.76	17.08	18.51	20.24
4 yrs and 6 to <12 months	13.71	14.50	15.42	16.62	18.09	19.71	21.72
5 yrs and 0 to <6 months	14.37	15.23	16.24	17.56	19.17	20.95	23.15
5 yrs and 6 to < 2 months	15.03	16.02	17.17	18.63	20.36	22.19	24.33
6 yrs and 0 to <6 months	15.55	16.84	18.24	19.91	21.70	23.43	25.25

Note: The adjusted age (Section 3.2.5.2) at the assessment/visit will be used to determine within which percentile the subject is included

Table 12–5: Body Weight Values (kg) by Age in Months/Years and Months for Females

Age	Percentile						
	3	10	25	50	75	90	97
6 to <7 months	6.06	6.49	6.95	7.47	8.02	8.53	9.05
7 to <8 months	6.32	6.75	7.21	7.75	8.31	8.83	9.37
8 to <9 months	6.53	6.97	7.43	7.97	8.54	9.08	9.63
9 to <10 months	6.71	7.15	7.62	8.17	8.74	9.29	9.85
10 to <11 months	6.86	7.31	7.78	8.34	8.93	9.49	10.06
11 to <12 months	7.02	7.46	7.95	8.51	9.11	9.68	10.27
1 yr and 0 to <1 month	7.16	7.62	8.11	8.68	9.29	9.87	10.48
1 yr and 1 to <2 months	7.31	7.77	8.27	8.85	9.47	10.07	10.69
1 yr and 2 to <3 months	7.46	7.93	8.43	9.03	9.66	10.27	10.90
1 yr and 3 to <4 months	7.61	8.08	8.60	9.20	9.85	10.47	11.12
1 yr and 4 to <5 months	7.75	8.24	8.76	9.38	10.04	10.67	11.33
1 yr and 5 to <6 months	7.90	8.39	8.93	9.55	10.23	10.87	11.55
1 yr and 6 to <7 months	8.05	8.55	9.09	9.73	10.42	11.08	11.77
1 yr and 7 to <8 months	8.20	8.71	9.26	9.91	10.61	11.28	11.99
1 yr and 8 to <9 months	8.34	8.86	9.43	10.09	10.81	11.49	12.21
1 yr and 9 to <10 months	8.49	9.02	9.59	10.27	11.00	11.70	12.44
1 yr and 10 to <11 months	8.64	9.18	9.76	10.46	11.20	11.92	12.67
1 yr and 11 to <12 months	8.78	9.34	9.93	10.64	11.40	12.13	12.90
2 yrs and 0 to <6 months	9.30	9.89	10.53	11.29	12.11	12.90	13.73
2 yrs and 6 to <12 months	10.18	10.85	11.56	12.43	13.36	14.27	15.23
3 yrs and 0 to <6 months	11.04	11.76	12.56	13.53	14.59	15.64	16.76
3 yrs and 6 to <12 months	11.83	12.61	13.49	14.56	15.75	16.95	18.27
4 yrs and 0 to <6 months	12.56	13.39	14.33	15.51	16.84	18.21	19.73
4 yrs and 6 to <12 months	13.27	14.15	15.15	16.41	17.89	19.43	21.20
5 yrs and 0 to <6 months	14.01	14.92	15.97	17.32	18.93	20.65	22.69
5 yrs and 6 to <12 months	14.81	15.75	16.84	18.27	20.00	21.91	24.22
6 yrs and 0 to <6 months	15.71	16.68	17.81	19.31	21.15	23.21	25.77

Note: The adjusted age (Section 3.2.5.2) at the assessment/visit will be used to determine within which percentile the subject is included.

13 EudraCT TABLE

A table Discontinuation due to AEs for the ES presents the number and percentage of subjects reporting an AE leading to discontinuation in the following categories:

- Total
- Serious fatal AE(s)
- Non-serious fatal AE(s)
- Non-fatal SAE(s)
- Non-serious non-fatal AE(s)
- Fatal SAE(s) and non-serious fatal AE(s)
- Fatal SAE(s) and non-fatal SAE(s)
- Fatal SAE(s) and non-serious non-fatal AE(s)
- Non-serious fatal AE(s) and non-fatal SAE(s)
- Non-serious fatal AE(s) and non-serious non-fatal AE(s)
- Non-fatal SAE(s) and non-serious non-fatal AE(s)
- Fatal SAE(s) and non-serious fatal AE(s) and non-fatal SAE(s)
- Fatal SAE(s) and non-serious fatal AE(s) and non-serious non-fatal AE(s)
- Fatal SAE(s) and non-fatal SAE(s) and non-serious non-fatal AE(s)
- Non-serious fatal AE(s) and non-fatal SAE(s) and non-serious non-fatal AE(s)
- Fatal SAE(s) and non-serious fatal AE(s) and non-fatal SAE(s) and non-serious non-fatal AE(s)

Note: A subject can only appear in 1 category. One subject can have more than 1 AE leading to discontinuation and therefore several criteria might have been met.
Note: This table uses AEs, not TEAEs.
Note: This table, with all the above categories, was created additionally to meet EudraCT requirements.
Note: this table will use data from subjects on adjunctive therapy as well as from subjects on monotherapy.

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

14.1 Amendment 1

The main purpose for the SAP amendment 1 is to apply the modifications according to the draft Protocol Amendment 3 dated on 04 Jun 2019. Moreover, many technical and detailed descriptions for executing the statistical analysis have been added in existing or new sections.

14.2 Amendment 2

Rationale for the amendment:

The SAP amendment 2 is aimed to apply the updates according to the final Protocol Amendment 3 dated on 29 Jan 2020. The purpose of Protocol Amendment 3 is to change the primary efficacy variable from daily partial seizure frequency monitored by 48h video-EEG to partial seizure frequency per week from Baseline to Visit 6 as agreed with PMDA.

Modifications and changes:

Change #1:

Section 1: Introduction

…. For regulatory purposes, a planned data cut-off will be made when the final subject who completes the Evaluation Period reaches Visit 13 and the final subject who directly enrolled in the Maintenance Period reaches Visit 14 in order to obtain 6-month exposure data.

Has been changed to

… For regulatory purposes, a planned data cut-off will be made when the final subject who completes the Evaluation Period reaches Visit 13 ~~and the final subject who directly enrolled in the Maintenance Period reaches Visit 14~~ in order to obtain 6-month exposure data.

Change #2:

Section 2: Protocol Summary

Amendment 3: 04 Jun 2019

Has been changed to

Amendment 3: 29 Jan 2020

Change #3:

Section 2.1.1 Primary Objective

The primary objective of this study is to confirm the efficacy of Levetiracetam (LEV) in the First Period based on the 48h video-EEG compared to historical control as adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures.

Has been changed to

The primary objective of this study is to confirm the efficacy of Levetiracetam (LEV) in reducing seizure frequency in the in the First Period ~~based on the 48h video-EEG~~ compared to historical control as adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures.

Change #4:

Section 2.1.2 Secondary Objective

The second and fourth bullets

- To evaluate the efficacy of LEV in the First Period based on the 48h video-EEG compared to historical control as monotherapy in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate the efficacy of LEV in the combined First and Second Periods based on the daily record card (DRC) as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

Has been changed to

- To evaluate the efficacy of LEV in reducing seizure frequency in the First Period compared to historical control as monotherapy in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate the efficacy of LEV in the combined First and Second Periods as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

Change #5:

Section 2.2: Efficacy variables

2.2.1 Efficacy variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

2.2.1.1 Efficacy variables for subjects on adjunctive therapy

2.2.1.1.1 Primary efficacy variable

First Period

The primary efficacy variable for the First Period for subjects on adjunctive therapy is the percent reduction in average daily frequency (ADF) of partial seizure frequency (ie, change from

the Selection Period to the Evaluation Period in daily partial seizure frequency monitored by the 48h video-EEG in their ADF) at Visit 6.

Combined First and Second Periods

There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

2.2.1.1.2 Secondary efficacy variables

First Period

The secondary efficacy variables for the First Period are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4
- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline at Visit 4, Visit 5, and Visit 6

Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

2.2.1.1.3 Other efficacy variables

First Period

The other efficacy variables for the First Period are the following:

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period

Combined First and Second Periods

There are no other efficacy variables for the combined First and Second Periods

2.2.1.2 Efficacy variables for subjects on monotherapy

2.2.1.2.1 Primary efficacy variable

There is no primary efficacy variable for subjects on monotherapy.

2.2.1.2.2 Secondary efficacy variables

First Period

The secondary efficacy variables for the First Period are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6

Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

2.2.1.2.3 Other efficacy variables

First Period

The other efficacy variables for the First Period are the following:

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period

Combined First and Second Periods

The other efficacy variable for the combined First and Second Periods is the following:

- Subjects who are continuously 6-month seizure-free monitored by the patient diary during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Has been changed to

2.2.1 Efficacy variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

2.2.1.1 Efficacy variables for subjects on adjunctive therapy

2.2.1.1.1 Primary efficacy variable

First Period

The primary efficacy variable for subjects on adjunctive therapy is the percent reduction in partial seizure frequency per week from Baseline to Visit 6.

Combined First and Second Periods

There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

2.2.1.1.2 Secondary efficacy variables

First Period

The secondary efficacy variable for the First Period is the following:

- Percent reduction in partial seizure frequency per week from Baseline to Visit 4 and Visit 5

Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in partial seizure frequency per week from Baseline
- For each visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

2.2.1.1.3 Other efficacy variables

First Period

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded through Protocol Amendment 2 are the following:

- Percent reduction in average daily frequency (ADF) of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all type of seizure frequency per week from Baseline
- For each visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

2.2.1.2 Efficacy variables for subjects on monotherapy

2.2.1.2.1 Primary efficacy variable

There is no primary efficacy variable for subjects on monotherapy.

2.2.1.2.2 Secondary efficacy variables

First Period

There is no secondary efficacy variable for the First Period.

Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in partial seizure frequency per week from Baseline
- For each visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

2.2.1.2.3 Other efficacy variables

First Period

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all types of seizure frequency per week from Baseline
- For each visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

- Percentage of subjects who are continuously 6-month seizure-free monitored by the patient diary 4.3

Change #6:

Section 4.3: Safety variables

2.2.3 Safety variables

2.2.3.1 Primary safety variable

There is no primary safety variable.

2.2.3.2 Secondary safety variables

The secondary safety variables for the First Period are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs led to discontinuation

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs leading to discontinuation

2.2.3.3 Other safety variables

The other safety variables are the following:

- Adverse events (variables other than secondary safety variables)
- Laboratory tests (blood chemistry and hematology)
- Vital signs
- Body weight and height
- Physical and neurological examination

Has been changed to

2.2.3 Safety variables

2.2.3.1 Primary safety variable

There is no primary safety variable.

2.2.3.2 Secondary safety variables

The secondary safety variables for the First Period are the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of serious adverse events (SAEs)

- Incidence of TEAEs leading to discontinuation from study medication

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs leading to discontinuation from study medication

2.2.3.3 Other safety variables

The other safety variables are the following:

- Adverse events (AEs) (variables other than secondary safety variables)
- Laboratory tests (blood chemistry and hematology)
- Vital signs
- Body weight and height
- Physical and neurological examination

Change #7:

Section 2.3: Study Design and Conduct

EP0100 is an open-label, single-arm, multicenter study with LEV as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV (14mg/kg/day to 42mg/kg/day for subjects aged at 1 month to <6 months, 20mg/kg/day to 60mg/kg/day for subjects aged at 6 months to <4 years) in the treatment of partial seizures over the 6-week Evaluation Period (First Period), followed by the long-term follow-up (Second Period) in pediatric subjects.

Subjects with uncontrolled partial seizures will be enrolled into the Selection Period. If all inclusion criteria, with the exception of the seizure criterion for 48h video-EEG, and none of the exclusion criteria are met, eligible subjects will be hospitalized and a 48h video-EEG performed. Subjects with at least 2 partial seizures during the Selection Period 48h video-EEG will enter the Evaluation Period. Subjects with <2 partial seizures during the Selection Period 48h video-EEG will enter the Maintenance Period.

…

No interim analysis is planned.

Has been changed to

EP0100 is an open-label, single-arm, multicenter study with LEV as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV (14mg/kg/day to 42mg/kg/day for subjects aged at 1 month to <6 months, 20mg/kg/day to 60mg/kg/day for subjects aged at 6 months to <4 years) in the treatment of partial seizures over the First Period (6 weeks), followed by the long-term follow-up (Second Period) in pediatric subjects.

…

~~No interim analysis is planned.~~

Change #8:

2.3.1 Study Periods

Retrospective Baseline Period

In order to evaluate the efficacy of LEV by the patient diary, seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline Period.

- First Period
  - Selection Period (maximum of 9 days)
  - Evaluation Period (6 weeks)

At Visit 6 the subject may enter the Second Period, or enter the Down Titration Period followed by the Safety Follow-Up Period:

  - Down-Titration Period (up to 4 weeks)
  - Safety Follow-Up Period (2 weeks)
- Second Period
  - Dose adjustment Period (6 weeks) (only for directly enrolled subjects [ie, 48h video-EEG failures])
  - Maintenance Period (until approval or the program is discontinued)
  - Down-Titration Period (up to 4 weeks)
  - Safety Follow-Up Period (2 weeks)

Has been changed to

2.3.1 Study Periods

Retrospective Baseline Period

~~In order to evaluate the efficacy of LEV by the patient diary,~~ Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline Period.

- First Period
  - Selection Period (maximum of 9 days)
  - Evaluation Period (6 weeks)

~~At Visit 6 the subject may enter the Second Period, or enter the Down Titration Period followed by the Safety Follow-Up Period:~~

  - Down-Titration Period (up to 4 weeks)
  - Safety Follow-Up Period (2 weeks)

- Second Period
  - ~~Dose adjustment Period (6 weeks) (only for directly enrolled subjects [ie, 48h video-EEG failures])~~
  - Maintenance Period (until approval or the program is discontinued)
  - Down-Titration Period (up to 4 weeks)
  - Safety Follow-Up Period (2 weeks)

Change #9:

2.4 Determination of Sample Size

…

The planned number of monotherapy subjects will be a total of 10 subjects.

Has been changed to

2.4 Determination of Sample Size

…

~~The planned number of monotherapy subjects will be a total of 10 subjects.~~

Due to the change in the primary efficacy variable in protocol amendment 3, the sample size was reconsidered. When the placebo rate area is conservatively redefined as ≤15% and assuming there are no nonevaluable subjects, a sample size of 38 subjects will obtain ≥80% power. Therefore, no change in sample size is required.

Change #10:

3.2.2 Schedule of Study Assessments

The study protocol gives the overall study schedule and the permissible intervals for these visits expressed as the number of days relative to Visit 3: Section 5.2 of protocol.

Table 3–1 presents the assessment schedule for subjects who are not 48h video-EEG failures and who are 48h video-EEG failures.

Table 14–1: Assessment Schedule

Study Visit	Target day*	Visit Window	Week number
Subjects who are not 48h video-EEG failures			
Evaluation Period			
Visit 3	Day 1		Week 0
Visit 4	Day 15	Day 11 to Day 19	Week 2
Visit 5	Day 29	Day 25 to Day 33	Week 4
Visit 6	Day 43	Day 39 to Day 47	Week 6
Maintenance Period			
Visit 8	Day 71	Day 64 to Day 78	Week 10
Visit 10	Day 99	Day 92 to Day 106	Week 14
Visit 11	Day 127	Day 120 to Day 134	Week 18
Visit 12	Day 155	Day 148 to Day 162	Week 22
Visit 13	Day 183	Day 176 to Day 190	Week 26
Visit 15	Day 267	Day 260 to Day 274	Week 38
Visit 16	Day 351	Day 337 to Day 365	Week 50
Visit 17	Day 435	Day 421 to Day 449	Week 62
Every 12 weeks			
Subjects who are 48h video-EEG failures			
Dose Adjustment Period			
Visit 6	Day 1		Week 0
Visit 7	Day 15	Day 11 to Day 17	Week 2
Visit 8	Day 29	Day 25 to Day 33	Week 4
Visit 9	Day 43	Day 39 to Day 47	Week 6
Maintenance Period			
Visit 10	Day 57	Day 50 to Day 64	Week 8
Visit 11	Day 85	Day 78 to Day 92	Week 12
Visit 12	Day 113	Day 106 to Day 120	Week 16
Visit 13	Day 141	Day 134 to Day 148	Week 20
Visit 14	Day 183	Day 176 to Day 190	Week 26
Visit 15	Day 225	Day 221 to Day 232	Week 32
Visit 16	Day 309	Day 295 to Day 323	Week 44
Visit 17	Day 393	Day 379 to Day 407	Week 56
Every 12 weeks			

Note: the day of the first dose of study medication is defined as Study Day 1, while the day before the date of first dose of study medication is defined as Study Day -1 (there is no Study Day 0).
* Day relative to first study drug intake

In the event that more than 1 assessment occurs within a given visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

Table 3–2 presents the mapping of Study Visits to Analysis Visits for subjects who are not 48h video-EEG failures and for subjects who are 48h video-EEG failures. Analysis visits will be used for analysis of long-term safety and efficacy data.

Table 14–2: Analysis Visit Mapping Table

Analysis Visit	Week number	Relative day since first study drug intake	Analysis window	Subjects who are not 48h video-EEG failures Study Visit (Target day*)	Subjects who are 48h video-EEG failures Study Visit (Target day*)
Baseline			Until Relative Day 1		
Evaluation/Dose Adjustment/Maintenance Period					
0	0	1		Visit 3	Visit 6
1	2	15	2 – 22	Visit 4	Visit 7
2	4	29	23 – 36	Visit 5	Visit 8
3	6	43	37 – 50	Visit 6	Visit 9
4	8	57	51 – 64	-	Visit 10
5	10	71	65 – 78	Visit 8 (Day 71)	-
6	12	85	79 – 95	-	Visit 11 (Day 85)
7	15	106	96 - 116	Visit 10 (Day 99)	Visit 12 (Day 113)
8	18	127	117 – 137	Visit 11 (Day 127)	-
9	21	148	138 – 158	Visit 12 (Day 155)	Visit 13 (Day 141)
10	24	169	159 – 179	-	-
11	27	190	180 – 200	Visit 13 (Day 183)	Visit 14 (Day 183)
12	30	211	201 – 231	-	Visit 15 (Day 225)
13	36	253	232 – 295	Visit 15 (Day 267)	-
14	48	337	296 – 379	Visit 16 (Day 351)	Visit 16 (Day 309)
15	60	421	380 – 463	Visit 17 (Day 435)	Visit 17 (Day 393)
16	72	505	464 – 547	Visit 18 (Day 519)	Visit 18 (Day 477)
17	84	589	548 – 631	Visit 19 (Day 603)	Visit 19 (Day 561)
Every 12 weeks					
Down-titration Period					
EDV/EOS	-	-			
Safety Follow-Up Period					
SFU	-	-			

* Day relative to first study drug intake

In the event that more than 1 assessment occurs within a given analysis visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

Has been changed to

3.2.2 Schedule of Study Assessments

The study protocol gives the overall study schedule and the permissible intervals for these visits expressed as the number of days relative to Visit 3: Section 5.2 of protocol.

Subjects who were directly enrolled in the Second Period based on the protocol prior to Amendment 3 will also be included in the efficacy and safety analysis with remapping of visit numbers to correspond to the ones for subjects who enrolled in the First Period.

Table 3–1 presents the assessment schedule for subjects:

- who are enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures; or
- who are enrolled according to Protocol Amendment 3; or
- who are enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures

Table 14–1: Assessment Schedule

Study Visit	Target day*	Visit Window	Week number
Subjects: • **who are enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures or** • **who are enrolled according to Protocol Amendment 3**			
Evaluation Period			
Visit 3	Day 1		Week 0
Visit 4	Day 15	Day 11 to Day 19	Week 2
Visit 5	Day 29	Day 25 to Day 33	Week 4
Visit 6	Day 43	Day 39 to Day 47	Week 6
Maintenance Period			
Visit 8	Day 71	Day 64 to Day 78	Week 10
Visit 10	Day 99	Day 92 to Day 106	Week 14
Visit 11	Day 127	Day 120 to Day 134	Week 18
Visit 12	Day 155	Day 148 to Day 162	Week 22
Visit 13	Day 183	Day 176 to Day 190	Week 26
Visit 15	Day 267	Day 260 to Day 274	Week 38
Visit 16	Day 351	Day 337 to Day 365	Week 50
Visit 17	Day 435	Day 421 to Day 449	Week 62
Every 12 weeks			
Subjects: • **who are enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures**			
Dose Adjustment Period			
Visit 6	Day 1		Week 0
Visit 7	Day 15	Day 11 to Day 17	Week 2
Visit 8	Day 29	Day 25 to Day 33	Week 4
Visit 9	Day 43	Day 39 to Day 47	Week 6
Maintenance Period			
Visit 10	Day 57	Day 50 to Day 64	Week 8
Visit 11	Day 85	Day 78 to Day 92	Week 12
Visit 12	Day 113	Day 106 to Day 120	Week 16
Visit 13	Day 141	Day 134 to Day 148	Week 20
Visit 14	Day 183	Day 176 to Day 190	Week 26
Visit 15	Day 225	Day 221 to Day 232	Week 32
Visit 16	Day 309	Day 295 to Day 323	Week 44
Visit 17	Day 393	Day 379 to Day 407	Week 56
Every 12 weeks			

Table 14–1: Assessment Schedule

Study Visit	Target day*	Visit Window	Week number

Note: the day of the first dose of study medication is defined as Study Day 1, while the day before the date of first dose of study medication is defined as Study Day -1 (there is no Study Day 0).
* Day relative to first study drug intake

In the event that more than 1 assessment occurs within a given visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

Table 3–2 presents the mapping of Study Visits to Analysis Visits for subjects :

- who are enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures and for subjects ; or
- who are enrolled according to Protocol Amendment 3; or
- who are enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures.

Analysis visits will be used for analysis of long-term safety and efficacy data.

Table 14–2: Analysis Visit Mapping Table

Analysis Visit	Week number	Relative day since first study drug intake	Analysis window	Subjects enrolled prior to Protocol Amendment 3 and are not 48h video-EEG failures; or subjects who are enrolled according to Protocol Amendment 3 Study Visit (Target day[1])	Subjects enrolled prior to Protocol Amendment 3 and are 48h video-EEG failures Study Visit (Target day[1])
Retrospective Baseline[2]		-	2 weeks prior to Visit 1		
Baseline Period					
-1	-1	-9	-9 – 0	Visit 1 Visit 2[3]	Visit 1 Visit 2[3]
Evaluation/Dose Adjustment/Maintenance Period					
0[4]	0	1		Visit 3	Visit 6
1	2	15	2 – 22	Visit 4	Visit 7
2	4	29	23 – 36	Visit 5	Visit 8
3	6	43	37 – 50	Visit 6	Visit 9
4	8	57	51 – 64	-	Visit 10
5	10	71	65 – 78	Visit 8 (Day 71)	-
6	12	85	79 – 95	-	Visit 11 (Day 85)
7	15	106	96 - 116	Visit 10 (Day 99)	Visit 12 (Day 113)
8	18	127	117 – 137	Visit 11 (Day 127)	-
9	21	148	138 – 158	Visit 12 (Day 155)	Visit 13 (Day 141)
10	24	169	159 – 179	-	-
11	27	190	180 – 200	Visit 13 (Day 183)	Visit 14 (Day 183)
12	30	211	201 – 231	-	Visit 15 (Day 225)
13	36	253	232 – 295	Visit 15 (Day 267)	-
14	48	337	296 – 379	Visit 16 (Day 351)	Visit 16 (Day 309)
15	60	421	380 – 463	Visit 17 (Day 435)	Visit 17 (Day 393)

16	72	505	464 – 547	Visit 18 (Day 519)	Visit 18 (Day 477)
17	84	589	548 – 631	Visit 19 (Day 603)	Visit 19 (Day 561)
Every 12 weeks					
Down-titration Period					
EDV/EOS	-	-			
Safety Follow-Up Period					
Safety Follow-Up	-	-			

EDV= Early Discontinuation Visit; EOS= End of Study
[1] Day relative to first study drug intake
[2] Retrospective Baseline is only applicable to seizure count data. For other analyses the time window of "2 weeks prior to Visit 1" for baseline is not applied.
[3] Study Visit 2 is only applicable for those subjects enrolled prior to Protocol Amendment 3.
[4] Analysis visit 0 is not applicable to laboratory test since Week 0 is not scheduled for laboratory test.

Change #11:

3.2.4 Mapping of Assessments Performed at Early Discontinuation Visit

Efficacy and safety assessments at an Early Discontinuation Visit (EDV) that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. In the event that the subject discontinues between two scheduled visits the data from the EDV are presented with data corresponding to the next scheduled visit for the subject.

Has been changed to

3.2.4 Mapping of Assessments Performed at Early Discontinuation Visit

Efficacy and safety assessments at an Early Discontinuation Visit (EDV) that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. In the event that the subject discontinues between two scheduled visits the data from the EDV are presented with data corresponding to the next scheduled visit for the subject. For subjects who had more than one EDV because of the starting dose of the Down-Titration Period, only the first EDV will be mapped to the scheduled visit.

Change 12:

3.5 Analysis Sets

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:

- SS A1 [Safety Set (Adjunctive therapy, First Period), i.e. Safety Set for subjects on Adjunctive therapy during the First Period]
- SS M1 [Safety Set (Monotherapy, First Period)]
- SS A12 [Safety Set (Adjunctive therapy, combined First and Second Periods)]
- SS M12 [Safety Set (Monotherapy, combined First and Second Periods)]

• Full Analysis Sets:

- FAS A1 [Full Analysis Set (Adjunctive therapy, First Period), i.e., Full Analysis Set for subjects on Adjunctive therapy during the First Period]
- FAS M1 [Full Analysis Set (Monotherapy, First Period)]
- FAS A12 [Full Analysis Set (Adjunctive therapy, combined First and Second Periods)]
- FAS M12 [Full Analysis Set (Monotherapy, combined First and Second Periods)]

• Per Protocol Set (PPS)

• Pharmacokinetic Per-Protocol Set (PK-PPS)

- PK-PPS A12 [Pharmacokinetic-Per-Protocol Set (Adjunctive therapy, combined First and Second Periods)]
- PK-PPS M12 [Pharmacokinetic-Per-Protocol Set (Monotherapy, combined First and Second Periods)]

If not stated otherwise, presentation of:

• Disposition and important protocol deviations are based on the ES

• Demographics, other baseline characteristics, safety, and exposure data are based on the SS A12 and SS M12

• Efficacy data are based on the FAS A1, FAS M1, FAS A12, and FAS M12. Sensitivity analyses on the primary efficacy variable are repeated for the PPS

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects enrolled (which include all subjects screened) into the Selection Period.

3.5.2 Safety Set

First Period:

The SS A1 will include all enrolled subjects on adjunctive therapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

The SS M1 will include all enrolled subjects on monotherapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

Combined First and Second Periods:

The SS A12 will include all enrolled subjects on adjunctive therapy in the Evaluation, Dose adjustment and Maintenance Period who receive at least 1 dose of study medication in the Evaluation, Dose adjustment or Maintenance Period.

The SS M12 will include all enrolled subjects on monotherapy in the Evaluation, Dose adjustment and Maintenance Period who receive at least 1 dose of study medication in the Evaluation, Dose adjustment or Maintenance Period.

3.5.3 Full Analysis Set

First Period:

The FAS A1 will consist of all subjects in the SS A1 who entered the First Period, who receive adjunctive therapy, have at least 24h of usable video-EEG time in the Selection Period, with at least 2 partial seizures, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time or DRCs in the Evaluation Period.

The FAS M1 will consist of all subjects in the SS MM who entered the First Period, who receive monotherapy, have at least 24h of usable video-EEG time in the Selection Period, with at least 2 partial seizures, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time or DRCs in the Evaluation Period.

Combined First and Second Periods:

The FAS A12 will consist of all subjects in the SS A12 AND, (all subjects in the FAS A1 OR subjects who have at least baseline efficacy assessment and 1 post-baseline efficacy assessment from DRCs in the Dose-adjustment or Maintenance Period).

The FAS M12 will consist of all subjects in the SS M12 AND, (all subjects in the FAS A1 OR subjects who have at least baseline efficacy assessment and 1 post-baseline efficacy assessment from DRCs in the Dose-adjustment or Maintenance Period).

3.5.4 Per Protocol Set

The Per-Protocol Set (Adjunctive therapy and First Period) will consist of all subjects in the FAS A1 who have at least 24h of usable video-EEG time in the First Period, and do not have important protocol deviations that affect the primary efficacy variable in the Evaluation Period.

The PPS is not defined for monotherapy and first period, and for the combined first and second Periods.

3.5.5 Other analysis sets

The PK-PPS A12 will consist of all subjects in the SS A12 for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

The PK-PPS M12 will consist of all subjects in the SS M12 for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

Has been changed to

3.5 Analysis Sets

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:

- SS_A (Safety Set [Adjunctive therapy])
- SS_M (Safety Set [Monotherapy])

• Full Analysis Sets:
- FAS_A (Full Analysis Set [Adjunctive therapy])
- FAS_M (Full Analysis Set [Monotherapy])

• Pharmacokinetic Per-Protocol Set (PK-PPS)
- PK-PPS_A [Pharmacokinetic-Per-Protocol Set (Adjunctive therapy)]
- PK-PPS_M [Pharmacokinetic-Per-Protocol Set (Monotherapy)]

If not stated otherwise, presentation of:

• Disposition and important protocol deviations are based on the ES

• Demographics, other baseline characteristics, safety, and exposure data are based on the SS_A and SS_M

• Efficacy data are based on the FAS_A and FAS_M.

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects enrolled (which include all subjects screened) into the Selection Period.

3.5.2 Safety Set

The SS_A will include all enrolled subjects on adjunctive therapy who receive at least 1 dose of study medication in the Evaluation Period.

The SS_M will include all enrolled subjects on monotherapy who receive at least 1 dose of study medication in the Evaluation Period.

For subjects who were directly enrolled in the Second Period based on the protocol prior to Amendment 3, after re-mapping they will be considered as entering in the Evaluation Period if they receive at least 1 dose of study medication in the Dose Adjustment Period.

3.5.3 Full Analysis Set

The FAS_A will consist of all subjects in the SS_A who have at least 1 post-baseline efficacy assessment.

The FAS_M will consist of all subjects in the SS_M who have at least 1 post-baseline efficacy assessment.

3.5.4 Per Protocol Set

Not applicable.

3.5.5 Other analysis sets

The PK-PPS_A will consist of all subjects in the SS_A for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

The PK-PPS_M will consist of all subjects in the SS_M for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

Moreover, many technical and detailed descriptions for executing the statistical analysis have been added in existing or new sections.

Change 13:

Section 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

For subjects on adjunctive therapy, summary of demographic data and data from other baseline characteristics will be presented for not 48h Video-EEG failures and for 48h Video-EEG failures by age category and for all subjects combined (overall).

For subjects on monotherapy, summary of demographic data and data from other baseline characteristics will be presented for not 48h Video-EEG failures and for 48h Video-EEG failures for all subjects combined (overall).

Has been changed to

Section 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Summary tables and listings will be presented for subjects on adjunctive therapy and for subjects on monotherapy, separately.

~~For subjects on adjunctive therapy, summary of demographic data and data from other baseline characteristics will be presented for not 48h Video-EEG failures and for 48h Video-EEG failures by age category and for all subjects combined (overall).~~

~~For subjects on monotherapy, summary of demographic data and data from other baseline characteristics will be presented for not 48h Video-EEG failures and for 48h Video-EEG failures for all subjects combined (overall).~~

Change 14:

Section 6.8.1 Definitions and derivations

Identification of AEDs

Medications are regarded as AED if they meet one of the following criteria:

- At least one of the possible level 2 ATC codes is [redacted]
- On the Prior and Concomitant Medications CRF the item “Indication” contains one of the following text (case insensitive):
  - epilepsy
  - epileptic (except for the case that indication is “status epilepticus”, i.e. CMINDC=”STATUS EPILEPTICUS”)

- On the Prior and Concomitant Medications CRF the item "Core AED?" is checked
- The medication is documented on the History of Previous Antiepileptic Drug Treatment CRF module

Has been changed to

Identification of AEDs

Medications are potentially regarded as potential AED if they meet one of the following criteria:

- ~~At least one of the possible level 2 ATC codes is~~ [redacted]
- ~~On the Prior and Concomitant Medications CRF the item "Indication" contains one of the following text (case insensitive):~~
  - ~~epilepsy~~
  - ~~epileptic (except for the case that indication is "status epilepticus", i.e. CMINDC="STATUS EPILEPTICUS")~~
- On the Prior and Concomitant Medications CRF the item "Core AED?" is checked
- The medication is documented on the History of Previous Antiepileptic Drug Treatment CRF module

Based on the criteria above, UCB will perform the manual review to the name, frequency and formulation of the medications and to identify the AEDs in an external file which is regularly updated in the course of the study.

Change 15:

Section 7.1 Definitions and Derivations

Overall Period treatment compliance is added:

- Overall Period, Treatment compliance (%) will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\sum_{first\ day}^{last\ day}(\text{\# of actual administrations per day})}{\text{total \# of administrations planned during the time the subject was in the study}} \times 100$$

where "total # of administrations planned during the time the subject was in the study" is equal to the total number of administrations planned during first planned administration of study medication and last planned administration, or day of discontinuation which will be calculated as the duration of exposure to study medication in days ×2. In consideration of whether the first administration is taken in the morning or in the evening, please see Section 10.1.1.

Change 16:

8 EFFICACY ANALYSES

Global updates to change the primary efficacy variable from daily partial seizure frequency monitored by 48h video-EEG to partial seizure frequency per week from Baseline to Visit 6 as agreed with PMDA.

Change 17:

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1.2 Tables and Figures

Descriptive statistics of LEV observed plasma concentrations and dose-normalized LEV plasma concentrations are summarized per defined time window post-dose by age categories (1 month<=Age<6 months, 6 months<=Age<1 year, 1 year<=Age<2 years, 2 years<=Age<4 years) and dose levels per administration (10 mg/kg, 20 mg/kg, 30 mg/kg in aged subjects of 6 months and above, 7 mg/kg, 14 mg/kg, 21 mg/kg in aged subjects less than 6 months) for observed concentrations or all dose levels for dose-normalized concentrations in PK-PPS. The statistics are calculated only if at least 2/3 of the individual data at a specific sampling point are above or equal to the LLOQ.

Figures of the geometric means of LEV observed plasma concentrations vs. defined time window post-dose are presented by age categories and dose levels. These figures by dose levels are superimposed in a same graph for each age categories.

Figures of the geometric means of LEV dose-normalized plasma concentrations vs. defined time window post-dose are presented by age categories in a same graph.

Scatter plots of LEV observed plasma concentrations vs. time after dosing are presented by age categories and dose levels. In addition, these figures are superimposed on scatter plots of plasma concentration vs. time in N01223 and figures of LEV plasma concentration time profiles simulated based on the population PK model established in N01288. The data of LEV plasma concentrations and times in N01223 are provided from data management group in UCB and the simulated median, and 5 percentile and 95 percentile of LEV plasma concentrations and times are provided from M&S group in UCB to reconstruct N01223 graphs and N01288 simulated graphs.

As needed, population PK analysis will be planned and described in a separate data analysis plan.

Has been changed to

Descriptive statistics of LEV observed and dose-normalized plasma concentrations will be summarized per defined time window post-dose by age category (1 month<=Age<6 months, 6 months<=Age<1 year, 1 year<=Age<2 years, 2 years<=Age<4 years) and dose level per administration (10mg/kg, 20mg/kg, 30mg/kg in aged subjects of 6 months and above, 7mg/kg, 14mg/kg, 21mg/kg in aged subjects less than 6 months) in PK-PPS_A and PK-PPS_M. The statistics are calculated only if at least 2/3 of the individual data at a specific sampling point are above or equal to the LLOQ.

<u>Scatter plots of LEV observed plasma concentrations vs. time after last dosing will be presented by age category and dose level. Scatter plots for LEV observed plasma concentrations vs time</u>

after last dosing by dose level will be superposed with different symbols in a single graph for each age category.

Scatter plots of LEV observed plasma concentrations vs. time after last dosing will be presented by age category and dose group. Scatter plots for LEV observed plasma concentrations vs time post dose by dose group will be superposed with different symbols in a single graph for each dose group. The dose groups are defined as:

- low dose group, 7mg/kg in aged subjects less than 6 months and 10mg/kg in aged subjects of 6 months and above;
- middle dose group, 14mg/kg in aged subjects less than 6 months and 20mg/kg in aged subjects of 6 months and above;
- high dose group, 21mg/kg in aged subjects less than 6 months and 30mg/kg in aged subjects of 6 months and above

Scatter plots of LEV dose-normalized plasma concentrations vs. time after last dosing will be presented by age category and dose level. Scatter plots for LEV dose-normalized plasma concentrations vs time after last dosing by dose level will be superposed with different symbols in a single graph for each age category.

Another scatter plot for LEV dose-normalized plasma concentrations vs time after last dosing will be presented by age category and AED category with different symbols in a single graph.

Scatter plots for LEV dose-normalized plasma concentrations vs time post dose by age category will be superposed with a scatter plot for LEV dose-normalized plasma concentrations vs time pose dose in N01223 with different symbols in a single graph. Dose-normalization of LEV plasma concentrations in N01223 will be performed to 10mg/kg for a subject with a body weight less than 50kg and to 500mg for a subject with a body weight more than or equal to 50kg.

In addition, scatter plots for LEV dose-normalized plasma concentrations vs time pose dose will be superposed with simulated LEV plasma concentration-time profiles based on the population PK model established in N01288 by age category. The data of LEV plasma concentrations and times in N01223 and N01288 are provided from data management group in UCB.

Change 18:

10.1.1 Definitions and Derivations

…

Date of last administration of study medication – Date of first day of period +1.

If date of last administration of study medication is missing, the last complete administration date will be used.

For start and end dates of periods see Section 2.3.1 and Section 5.1.1.4 .

Details on study medication administration are recorded on the "Study Medication Administration – IV" and "Study Medication Administration – Dry Syrup" eCRFs.

Has been changed to:

Date of last administration of study medication – Date of first day of period +1.

If date of last administration of study medication is missing, the last complete administration date will be used.

For start and end dates of periods see Section 2.3.1 and Section 5.1.1.4 .

Details on study medication administration are recorded on the "Study Medication Administration – IV" and "Study Medication Administration – Dry Syrup" eCRFs.

The modal dose is calculated using the daily dose (morning dose + evening dose). If there are tied cases, the later dose will be the modal dose.

Change 19:

Section 10.2 Adverse Events

An overview of AEs presents number and percent of subjects with any TEAE, serious TEAEs, TEAEs leading to discontinuation, TEAEs requiring dose change, any ADR, severe TEAEs, as well as deaths together with the number of individual occurrences in those categories.

Incidences of TEAEs by SOC and PT are presented together with the number of individual occurrences for pre-treatment, TEAEs, ADRs, TEAEs and ADRs leading to temporary and/or permanent discontinuation, serious TEAEs and ADRs.

Additional tables are presented for TEAEs by intensity and for a subset of TEAEs occurring in at least 5% of subjects.

Has been changed to:

Section 10.2 Adverse Events

An overview of AEs presents number and percent of subjects with any TEAE, serious TEAEs, TEAEs leading to discontinuation, TEAEs requiring dose change, any drug-related TEAEs, severe TEAEs, as well as deaths together with the number of individual occurrences in those categories.

Incidences of TEAEs by SOC and PT are presented together with the number of individual occurrences for , TEAEs, , serious TEAEs and serious drug-related TEAEs, and TEAEs leading to discontinuation of study drug.

Additional tables are presented for TEAEs by intensity and for a subset of TEAEs occurring in at least 5% of subjects.

Change 19:

10.2.1.5 Adverse Drug Reactions

Adverse drug reactions (ADRs), a subset of TEAEs, are identified using information documented on the AE CRF. “Relationship to Study Medication” is documented as “related” or missing.

Has been changed to:

This section is removed from the SAP Amendment 2.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

Approval Signatures

Name: EP0100-SAP Amendment 3

Version: 1.0

Document Number: CLIN-000188865

Title: EP0100-SAP Amendment 3

Approved Date: 05 May 2022

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-May-2022 02:06:04 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-May-2022 13:23:21 GMT+0000