STATISTICAL ANALYSIS PLAN

Study: EP0083

Product: Brivaracetam

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ADJUNCTIVE BRIVARACETAM IN SUBJECTS (≥16 TO 80 YEARS OF AGE) WITH PARTIAL SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

SAP/Amendment Number	Date
Final SAP	24 Nov 2017
SAP Amendment 1	03 Oct 2019
SAP Amendment 2	09 Jun 2022
SAP Amendment 3	17 Aug 2022

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ANCOVA	analysis of covariance
BMI	body mass index
BRV	brivaracetam
CI	confidence interval
$Conc_{norm}$	Dose-normalized plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	coefficient of variation
DBP	diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	electrocardiogram
EEG	electroencephalography
CRF	case report form
EDV	Early Discontinuation Visit
ES	Enrolled Set
FAS	Full Analysis Set
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IPD	important protocol deviation
KM	Kaplan–Meier
LEV	levetiracetam
LLOQ	lower limit of quantification
LTFU	long-term follow-up
MAP	managed access program
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PBO	placebo
PCST	possibly clinically significant treatment-emergent
PDILI	potential drug-induced liver injury

PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set
PT	preferred term
RS	Randomized Set
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SS	Safety Set
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 final clinical study report (CSR). The SAP is based on the following study document: Protocol Amendment 4 (10 Jan 2020) and Protocol Amendment 4.1 (07 Feb 2020).

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To evaluate the efficacy of brivaracetam (BRV) compared to placebo (PBO) as adjunctive treatment in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization despite current treatment with 1 or 2 concomitant antiepileptic drugs (AEDs).

2.1.2 Secondary objectives

The secondary objectives are to assess the safety and tolerability of BRV in subjects ≥16 years to 80 years of age.

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable is the partial seizure frequency per 28 days during the 12-week Treatment Period.

2.2.1.2 Secondary efficacy variables

Secondary efficacy variables are as follows:

- The 50% responder rate based on percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period
- Percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period
- Categorized percent reduction in partial seizures frequency per 28 days from Baseline to the 12-week Treatment Period
- All seizure frequency (partial, generalized, and unclassified epileptic seizures) per 28 days during the 12-week Treatment Period
- Seizure freedom (partial, all epileptic seizures) during the 12-week Treatment Period
- Time to n^{th} (n=1, 5, 10) partial seizure during the 12-week Treatment Period

2.2.2 Pharmacokinetic variable

The pharmacokinetic (PK) variable is BRV (parent compound only) plasma levels.

2.2.3 Primary safety variables

The primary safety variables are as follows:

- Incidence of treatment-emergent adverse events (TEAE)
- Incidence of TEAEs leading to study withdrawal
- Incidence of treatment-emergent serious adverse events (SAEs)

2.2.4 Other safety variables

The other safety variables are as follows:

- Changes in clinical laboratory test parameters (blood chemistry, hematology, urinalysis)
- Change in electrocardiogram (ECG) parameters and findings
- Changes in vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate]
- Changes in body weight
- Physical examination
- Neurological examination
- Mental status
- Psychiatric status

2.3 Study design and conduct

This is a randomized, double-blind, PBO-controlled, multicenter, therapeutic confirmatory study evaluating 2 doses of BRV. The subject population will be subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. Subjects who are not legal adults will be included only where legally permitted and ethically accepted.

Subjects will complete an 8-week prospective Baseline Period, followed by a 12-week Treatment Period. Subjects may be eligible for conversion to a long-term follow-up (LTFU) study or managed access program (MAP) upon completion of the Treatment and Transition Period. Subjects who are assigned to enter MAP but who cannot directly convert to MAP will be assigned to an Open-Label Temporary Period until the date when the subjects can convert to MAP. There is a 4-week Down-Titration Period followed by a 2-week Study Drug-Free Period for subjects not entering the LTFU study or MAP. If BRV is commercially available upon subject completion of the Treatment and Transition Periods, subjects will receive BRV directly without entering the LTFU study or MAP.

A 1:1:1 central randomization (random permuted blocks) stratified for country, levetiracetam (LEV) use (LEV naïve versus prior LEV use), and number of AEDs previously used but discontinued prior to study entry (≤2 versus >2 AEDs) will be used to ensure the balance across treatment groups (PBO, BRV 50mg/day, BRV 200mg/day) within each combination of stratification levels. Randomization will not be stratified by study center due to the expected small number of randomized subjects per study center.

No restrictions are placed on the proportion of randomized subjects within each stratification level, either overall or on a regional basis.

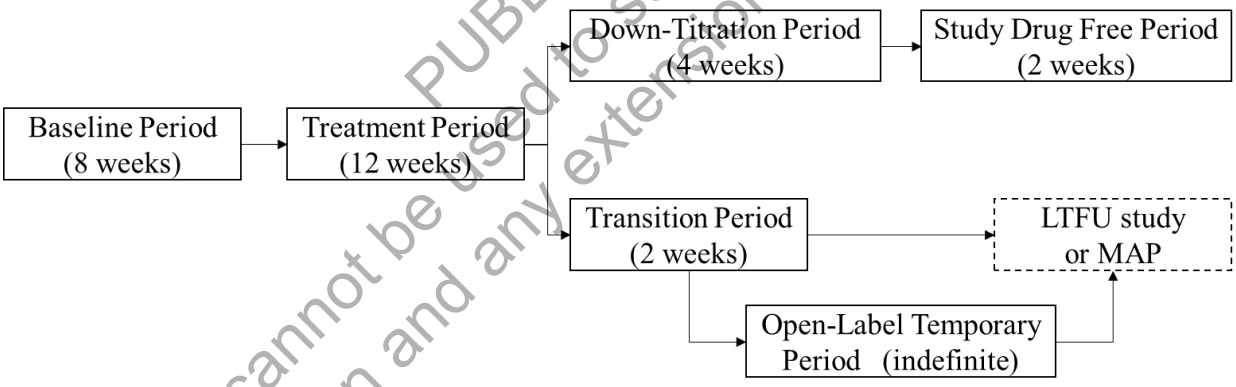
2.3.1 Study duration per subject

Aside from the Open-Label Temporary Period, the total duration of the study will be up to approximately 26 weeks with a maximum 16-weeks exposure to BRV consisting of the following study periods:

- Baseline Period (8 weeks)
- Treatment Period (12 weeks)
- Down-Titration Period (4 weeks)
- Study Drug-Free Period (2 weeks)
- Transition Period (2 weeks) (required for subjects participating in the LTFU study or MAP)
- Open-Label Temporary Period (for subjects who are assigned to enter MAP but who cannot directly convert to MAP; starts after the end date of the Transition Period and continues until date when subject can convert to MAP, BRV is commercially available or until UCB decides to close the study)

A schematic diagram of study periods is shown in Figure 2-1.

Figure 2-1 Schematic diagram of study periods



Ideally, visits should occur on the specified Visit/Week. A ±3 days window for each specified Visit/Week is allowed, provided the subject has adequate investigational medicinal product (IMP) to sustain the visit window.

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

2.3.2 Planned number of subjects and sites

The planned number of evaluable subjects for the primary efficacy analysis is 444 (148 subjects per treatment group). The number of prior LEV use subjects will be limited to 30% of the total study population. Considering an anticipated screen failure rate of approximately 20%, approximately 555 subjects were to be screened. It is planned to have subjects recruited in approximately 95 sites.

2.3.3 Anticipated regions and countries

The study is being conducted in Japan, Taiwan, China Mainland, Philippines, Thailand, Singapore, and Malaysia.

2.4 Determination of sample size

A total of 148 analyzable subjects per treatment group will provide 80% power to simultaneously detect differences between BRV treatment groups (BRV 50mg/day group and BRV 200mg/day group) and the PBO group at the 1-sided 0.025 significance level. The sample size assumes treatment differences of 0.221 and 0.285 in means on the log-transformed scale and a common SD of 0.66. The estimates of 0.221 and 0.285 correspond to reductions of 19.8% and 24.8% of BRV over PBO after back-transformation, respectively. The percent reduction of 24.8% is obtained from BRV 200mg/day in the N01358 study and assuming the LEV cap of 30% is reached overall. Based on a similar result from the Integrated Summary of Efficacy and again assuming the LEV cap of 30% is reached overall, a 19.8% reduction of BRV 50mg/day over PBO can be estimated. The SD of 0.66 is based on the observed SD from all treatment groups in N01358. The sample size calculation accounts for the correlation of the test statistics (same placebo group is compared to each BRV dose) as well as the planned Hochberg procedure. A total of 444 (148×3) analyzable subjects in the study is calculated as a target number.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be carried out using SAS® Version 9.3 or higher. Descriptive statistics, such as the number of subjects with available measurement (*n*), mean, SD, median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Unless otherwise noted, denominator for percentages will generally be based on the set of subjects with at least 1 assessment at the time point or at least 1 assessment during the time interval being summarized.

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

- "*n*" will be an integer
- Mean, SD, median, 25th percentile and 75th percentile will use 1 additional decimal place compared to the original data.
- Minimum and maximum will have the same number of decimal places as the original value.

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%. All statistical testing will be carried out at a two-sided 0.05 significance level unless otherwise indicated. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999". The rounded value of p-values ≥0.0001 and ≤0.9999 will be displayed. P-values exactly equal to 1 should be shown as 1.0000.

Summaries for disposition, important protocol deviations, demographics and other baseline characteristics, medical history, and prior and concomitant medications (AEDs and non-AEDs) will present results for individual treatment groups, for both BRV groups combined, and all

treatment groups combined. Summaries of seizure outcomes will present results for individual treatment groups only. Summaries of safety outcomes will present results for individual treatment groups and for both BRV groups combined. Summaries of IMP (including study medication duration, cumulative duration, and compliance) will present results for individual treatment groups and for both BRV groups combined. Summaries of PK will present results for individual BRV treatment group only.

Statistical outliers are defined as values that are discordant with other values and are clinically implausible. Exclusion of outliers from an analysis requires thorough justification based on statistical and clinical grounds. Any outliers will be reviewed during the data evaluation meeting (DEM) prior to database lock. Subject data listings will be provided and will present source data and key derived variables for statistical analyses.

Generally, the Down-Titration Period follows the Treatment Period, but it is also possible that down-titration is carried out during the Transition Period or the Open-Label Temporary Period. In the cases of the down-titration during the Transition Period, it will be handled as same as that after the Treatment Period. The BRV dose may be decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 25mg/day (morning dose only) for one week should be included.

Tables for the Open-Label Temporary Period will be created separately from those for other periods unless stated otherwise.

All summary tables and figures will be presented overall and by Japan, unless stated otherwise. In addition, by-region subgroup analysis will be performed overall, by Japan, and by Non-Japan to the selected efficacy endpoints (see Section 4.7).

3.1.1 Statistics for BRV plasma concentrations

For BRV plasma concentration (µg/mL) and daily dose-normalized (to 50mg) BRV plasma concentrations ($Conc_{norm}$, in µg/mL), descriptive statistics include number of values, number of values above or equal to the lower limit of quantification (LLOQ), geometric mean, geometric 95% confidence interval (CI), geometric coefficient of variation (CV), arithmetic mean, SD, median, minimum, and maximum. For the calculation of descriptive statistics, a BRV plasma concentration below LLOQ is substituted by LLOQ/2.

- $Conc_{norm}$ is derived as follows;

$$\text{Conc}_{\text{norm}} = \frac{\text{Concentration} \times 25}{\text{Actual dose/administration (mg)}}.$$

- Geometric 100×(1- α/2)% CI is constructed using the following formula;

$$[e^{(m-\text{t}(1-\alpha/2,n-1)\times \text{SD}/\sqrt{n},)}, e^{(m+\text{t}(1-\alpha/2,n-1)\times \text{SD}/\sqrt{n})}],$$

  where m and SD are the arithmetic mean and standard deviation of the log transformed BRV plasma concentrations for a time point, respectively. Furthermore t(1-α/2, n-1) is the 100×(1-α/2) percentile of the t-distribution with n-1 degrees of freedom.

  Lower and upper limits of CI are presented using significant digits same as the corresponding geometric mean.

- Geometric CV (%) is calculated using the following formula;

$$\text{geometric CV}(\%) = \sqrt{e^{\text{SD}^2} - 1} \times 100,$$

where SD is the standard deviation from the log-transformed data.

Geometric CV (%) is presented to one decimal place.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day

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

3.2.2 Study periods

All measurements will be classified into study periods as follows:

Baseline Period	From the date of Visit 1 prior to the date of Visit 3.
Treatment Period	From the date of Visit 3 until the day of Visit 7 in subjects who complete the Treatment Period; or EDV in subjects who discontinue treatment early prior to Visit 7. A subject is considered starting Treatment Period if the subject enters Visit 3 and is randomized. If a subject does not have a Visit 7 or EDV date, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of IMP during the Treatment Period, whichever is later, will define the end date of the Treatment Period.
Down-Titration Period	From immediately after the last visit of the Treatment Period (Visit 7 or EDV) until Visit 8 for subjects who take any IMP during the Down-Titration Period. For subjects who enter the Down-Titration Period after the Transition Period without entering either LTFU study, MAP, or the Open-Label Temporary Period, it starts from immediately after the last visit of the Transition Period (Visit 8 Week 14).
Study Drug-Free Period	From immediately after the last visit of the Down-Titration Period until date of Safety Visit for subjects who enter the Down-Titration Period.
Transition Period	From immediately after the last visit of the Treatment Period (Visit 7 or EDV) until Visit 8 for subjects who take any IMP

	during the Transition Period and who are scheduled to enter LTFU study, MAP or Open-Label Temporary Period.
Open-Label Temporary Period	This period is only applicable for subjects who cannot convert to MAP due to delayed importation of medication. The period is defined from immediately after the last visit of the Transition Period (Visit 8) and until a visit when the subject can convert to MAP.

3.2.3 End of treatment value

The "End of treatment" value for laboratory tests, vital signs and ECG is a value collected in the last visit including unscheduled visits during the treatment period.

3.2.4 Actual stratification level per CRF

During the conduct of the randomization, some subjects with the stratification levels of LEV status or number of previous AEDs mistakenly entered to the IVRS system. The actual stratification level will be derived according to the CRF data:

The LEV status per CRF (LEV naïve vs prior LEV use) will be captured from the CRF form "History of Previous Antiepileptic Drug Treatment". Subjects will be considered with prior LEV use if levetiracetam is captured in any preferred drug name in this CRF form. Otherwise, the subjects will be considered LEV naïve.

The number of AEDs previously used but discontinued prior to study entry per CRF (≤2 vs >2 AEDs) will also be captured from the CRF form "History of Previous Antiepileptic Drug Treatment" by counting the number of unique AED entered in this form. However, if the same compound name is also entered in the CRF form "Prior and Concomitant Medications", the drug is not counted as a previous AED because it is considered that the subject has taken the same AED concomitantly during the study. This was instructed in the CRF completion instruction regarding how to count the number of previous AED at the randomization.

The following AEDs will be considered the same AED at the group level while counting the number of previous AEDs:

- Valproate includes valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, ergenyl chrono, valproic acid.
- Phenytoin includes phenytoin sodium, phenytoin calcium, mephenytoin, zentronal, metetoin, ethotoin, albutoin, hydantal, phelantin, hydantol D, anirrit, dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, hydantoin.
- Phenobarbital includes phenobarbital sodium, methylphenobarbital, metharbital, alepsal, phenobarbital, kaneuron, epanal.
- Benzodiazepine AEDs are grouped separately by bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate.

3.3 Definition of Baseline values

Baseline values will be determined from the last non-missing data collected prior to the first dose of IMP, unless otherwise noted for a specific type of data.

Baseline value for seizure frequency will be based on the 28-day adjusted seizure frequency calculated from daily record card (DRC) days over the Baseline Period. For seizures occurred on the date of Visit 3 will be entered to Visit 3 or Visit 4 CRF form "Seizure Count" depending on whether the seizure occurred before or after the randomization time. If the seizure occurred before the randomization, it would be entered to Visit 3 and counted as seizure at Baseline Period; if the seizure occurred after the randomization, it would be entered to Visit 4 and counted as seizure at Treatment Period. The calculation of 28-day adjusted frequency is described in detail in Section 3.9.3.

Baseline values for laboratory parameters, vital signs, body weight, and ECGs will be based on the latest scheduled or unscheduled assessment prior to or on the date of first administration of IMP. Baseline value will be determined separately for each individual clinical laboratory parameter for hematology, blood chemistry, and urinalysis assessments.

3.4 Important protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol that could potentially impact the interpretation of the study data. The criteria for identifying IPDs and the classification of IPDs will be defined separately in the Specifications for IPDs document. To the extent feasible, rules for identifying IPDs will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying IPDs will be implemented algorithmically to ensure consistency in the classification of IPDs across all subjects.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) consists of all screened subjects who gave informed consent (and informed assent where required). Subjects who discontinued due to screen failure are included in the ES. This analysis set is referred to as "All Subjects Screened".

3.5.2 Randomized Set

The Randomized Set (RS) consists of all subjects who were randomized to treatment.

3.5.3 Safety Set

The Safety Set (SS) will include all randomized subjects who received at least 1 dose of study medication. Safety analyses will be carried out using the SS.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of study drug and have at least 1 post-Baseline seizure daily record card (DRC) data during the Treatment Period. Both primary and secondary efficacy analyses will primarily be carried out using the FAS.

3.5.5 Per Protocol Set

The Per-Protocol Set (PPS) will consist of all subjects in the FAS who do not have any IPDs potentially impacting the primary efficacy variable. In order to verify the robustness of the efficacy results, the primary efficacy variable will also be analyzed using the PPS.

3.5.6 Pharmacokinetic Per Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects who took at least 1 dose of BRV and for whom at least 1 valid BRV plasma concentration-time record and dosing information are available.

3.6 Treatment assignment and treatment groups

All analyses will be based on randomized treatment group. Incorrectly treated subjects will be evaluated during the blinded DEM to assess the potential impact of such cases and any special considerations for statistical analyses. In general, subjects will be analyzed according to the planned treatment dose for efficacy analyses and according to the actual treatment dose for safety and PK analyses.

The labels used in presentations will be:

- BRV 200mg/day
- BRV 50mg/day
- Placebo (or PBO)
- All Subjects
- Not randomized
- All BRV (BRV 200mg/day + BRV 50mg/day)

3.7 Site pooling strategy

The number of randomized subjects for most investigator sites is expected to be low. In general, it will not be feasible to adjust statistical analyses for site effect and there are no plans to present any study outcomes by site. No site pooling strategy is defined 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 18.1. Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL) version SEP 2017. Medical procedures will not be coded.

3.9 Definitions of study-specific derived variables

3.9.1 Lengths of study periods

Number of days in Baseline Period = date of day before Visit 3 – date of Visit 1.

Note that the 0.5 day is attributed from the day of Visit 3 which is considered part of the Baseline Period, and 0.5 days from the day of Visit 1 which is also considered part of the Baseline Period

Number of days in Treatment Period = date of Visit 7 (or EDV) – date of Visit 3.

Note that the first and last day of treatment period are considered as half days.

A similar calculation formula to the Treatment Period is applied to other post-treatment periods.

3.9.2 Seizure frequency

Each seizure code in the clinical database will be mapped to exactly 1 of the following codes based on the International League Against Epilepsy (ILAE) classification (1981): IA (IA1, IA2, IA3, and IA4), IB, IC, II (IIA, IIB, IIC, IID, IIE, and IIF) or III.

With regard to cluster seizures, investigator sites are to report the number of cluster episodes rather than reporting the estimated number of individual seizures. Therefore, no imputation will be applied for the seizure counts corresponding to reports of cluster seizures. Namely, in all the efficacy analyses, each cluster episode will be counted as one seizure of reported seizure type.

The total number of seizures for seizure type I (IA+IB+IC) and the total number of seizures for all seizure types (I+II+III) will be calculated across all DRC data over the study period being summarized.

3.9.3 28-day adjusted seizure frequency and log-transformed seizure frequency

Twenty-eight day adjusted seizure frequency for partial seizures (seizure types IA+IB+IC), and for all seizure types (I+II+III) will be calculated for each study period by dividing the number of targeted seizures (partial seizures or all seizure types) by the number of days for which the DRC was completed for each study period, and multiplying the resulting value by 28.

The above values for each study period will be transformed using the function $\log(x+1)$, where log represents the natural logarithm function.

3.9.4 Seizure freedom during the Treatment Period

Seizure freedom is assessed for partial seizures and all epileptic seizures.

3.9.4.1 All epileptic seizures freedom

Subjects are defined as all epileptic seizure-free during the Treatment Period if they meet all of the following criteria.

1. The subject completed the Treatment Period, and
2. The subject did not have any missing days in the DRC over the Treatment Period, and
3. The subject did not report any seizures over the Treatment Period

Specific algorithmic rules for each of the above are defined as follows:

Criterion 1: A subject is defined as completing the Treatment Period if the subject completed all scheduled visits of Treatment Period (ie, Visit 4 to Visit 7).

Criterion 2: A subject meets criterion 2 if no "Not Done" dates were reported from Visit 4 up to Visit 7 in the Seizure Counts CRF module.

Note that the CRF module for Visit 4 covers seizure records from the afternoon at the date of Visit 3 up to the morning at the date of Visit 4, and that the module for Visit 7 covers seizure records from the afternoon at the date of Visit 6 up to the morning at the date of Visit 7.

Criterion 3: A subject meets criterion 3 if there are no records of seizures from Visit 4 up to Visit 7 in the Seizure Counts CRF module with either a count >0 or a reported seizure code with an unknown or missing seizure count.

3.9.4.2 Partial seizures freedom

Criteria 1 and 2 (see Section 3.9.4.1) are the same as for all epileptic seizure freedom. However, criterion 3 is modified to only include partial seizures.

3. The subject did not report any partial seizures over the Treatment Period

Criterion 3: A subject meets criterion 3 if there are no records of partial seizures from Visit 4 up to Visit 7 in the Seizure Counts CRF module with either a partial seizure frequency count >0 or a reported partial seizure code with an unknown or missing seizure count.

3.9.5 Time to n^{th} partial seizure

The evaluation of time to n^{th} partial seizure is based on the relative day of occurrence of the n^{th} partial seizure (n=1, 5, and 10) during the Treatment Period. Only seizure DRC data from the randomization up to and including the last visit of the Treatment Period will be considered. The algorithms described in Section 3.9.2 also apply to this analysis.

The time to n^{th} seizure will be calculated as the date of the n^{th} partial seizure minus the date of randomization plus 1 day for subjects who have at least n partial seizures in the Treatment Period. Subjects with fewer than n partial seizures during this period will be addressed as follows:

- Subjects who complete the Treatment Period will be analyzed as censored cases with date of censoring (ie, analyzed as non-events) based on the date of last dose of IMP during the Treatment Period.
- Subjects who discontinue due to lack of efficacy during the Treatment Period will be analyzed as having the n^{th} seizure (i.e. as an event) on the date of last dose of IMP during the Treatment Period.
- Subjects who discontinue for reasons other than lack of efficacy during the Treatment Period will be analyzed as censored cases with date of censoring based on the date of last dose of IMP during the Treatment Period.

For those cases, time to censoring or time to event will be calculated as the date of last dose of IMP during the Treatment Period minus the date of randomization plus 1 day.

3.9.6 Dose mapping for total daily BRV dose

During the Treatment Period, subjects are to take 3 tablets twice per day (morning and evening) except for the first day where they will only take the evening dose, and the last day where they will only take the morning dose.

The 3 tablets will consist of: 2 × 50mg BRV tablets and 1 × 25mg PBO tablet for subjects randomized to the BRV 200mg treatment group; 1 × 25mg BRV tablet and 2 × 50mg PBO

tablets for subjects randomized to the BRV 50mg treatment group; 2 × 50mg PBO tablets and 1 × 25mg PBO tablet for subjects randomized to the PBO group, as shown in Table 3.1.

Table 3.1: Doses of individual BRV and PBO tablets during the Treatment Period

Treatment group	Individual tablet contents and dose (mg)					
	Morning			Evening		
BRV 200mg/day	BRV 50	BRV 50	PBO 25	BRV 50	BRV 50	PBO 25
BRV 50mg/day	PBO 50	PBO 50	BRV 25	PBO 50	PBO 50	BRV 25
PBO	PBO 50	PBO 50	PBO 25	PBO 50	PBO 50	PBO 25

During the Transition Period subjects are to take 2 tablets twice per day (morning and evening) except for the first day where they will only take the evening dose, and the last day where they will only take the morning dose. The 2 tablets will consist of: 1 × 50mg BRV tablet and 1 × 25mg BRV tablet for subjects randomized to the BRV 200mg treatment group; 1 × 25mg BRV tablet and 1 × 50mg PBO tablet for subjects randomized to the BRV 50mg treatment group; 1 × 50mg PBO tablet and 1 × 25mg PBO tablet for subjects randomized to the PBO group, as shown in Table 3.2.

Table 3.2: Doses of individual BRV and PBO tablets during the Transition Period

Treatment group	Individual tablet contents and dose (mg)			
	Morning		Evening	
BRV 200mg/day	BRV 50	BRV 25	BRV 50	BRV 25
BRV 50mg/day	PBO 50	BRV 25	PBO 50	BRV 25
PBO	PBO 50	PBO 25	PBO 50	PBO 25

During the Down-Titration Period in weeks 1 to 3 subjects are to take 2 tablets twice per day (morning and evening) except for the first day where they will only take the evening dose, and the last day where they will only take the morning dose. In week 4 subjects will take 2 tablets in the morning only. The total dose of BRV will decrease each week, as shown in Table 3.3.

Table 3.3: Doses of individual BRV and PBO tablets during the Down-Titration Period

	Individual tablet contents and dose (mg)			
Treatment group	**Morning**		**Evening**	
BRV 200mg/day				
BRV 150mg/day (Week1)	BRV 50	BRV 25	BRV 50	BRV 25
BRV 100mg/day (Week 2)	BRV 50	PBO 25	BRV 50	PBO 25
BRV 50mg/day (Week 3)	PBO 50	BRV 25	PBO 50	BRV 25
BRV 25mg/day (Week4)	PBO 50	BRV 25	-	

	Individual tablet contents and dose (mg)			
Treatment group	**Morning**		**Evening**	
BRV 50mg/day				
BRV 25mg/day (Week1)	PBO 50	BRV 25	PBO 50	PBO 25
PBO (Week 2 & 3)	PBO 50	PBO 25	PBO 50	PBO 25
PBO (Week 4)	PBO 50	PBO 25	-	
PBO				
PBO (Week 1, 2 & 3)	PBO 50	BRV 25	PBO 50	PBO 25
PBO (Week 4)	PBO 50	PBO 25	-	

In the drug dosing log CRF the daily total blinded dose (BRV + PBO) is recorded. The appendix Section 12.1 describes how to determine the daily BRV dose and number of tablets taken using the total blinded dose for each treatment group. It should be noted that when a subject is on 200mg BRV or 50mg BRV treatment and if subject takes less than the number of tablets per day they are supposed to take, it is unknown whether they missed an active or placebo treatment. It is assumed that the subject took the active treatment before PBO. For example, suppose a BRV 200mg subject used 3 tablets on a study day during the Treatment Period, and this day was not their first or last day during the Treatment Period, it would be assumed that the subject used the 3 × 50mg BRV tablets so would have a BRV quantity of 150mg BRV tablets.

If a subject on 200mg BRV or 50mg BRV treatment exceeds the number of tablets per day they are supposed to take, it is assumed they begin retaking the tablets for the same study day, and it is assumed that the subject took active treatment before PBO for the additional tablets. For example, suppose a BRV 200mg subject used 7 tablets on a study day during the Treatment Period, and this day was not their first or last day during the treatment period, it would be assumed that the subject used the 4 × 50mg BRV tablets and 2 PBO tablets they were supposed to take on the study day, and an additional active treatment of 50mg so they would have a BRV quantity of 250mg BRV tablets.

In the circumstance the daily total blinded dose as recorded on the CRF exceeds the maximum nominal dose as described in the appendix Section 12.1, it is assumed the subject took the active treatment for all additional dosage. For example, suppose a BRV 200mg subject was recorded 275 mg/day total daily dose during the treatment period on the CRF (exceeding the maximum dose of 200 mg/day during the treatment period), it would be assumed the subject took active 200mg + 75 mg =275 mg/day.

3.10 Changes to protocol-defined analyses

Not applicable

3.11 Consideration for COVID-19

A new COVID-19 CRF, to evaluate the impact of global pandemic was created and implemented to collect the information on impacted visit, impact category, and relationship to COVID-19.

The relationship to COVID-19 global pandemic will be assessed and captured in CRF form COVID-19 Impact: “Relationship to COVID-19” as: confirmed COVID-19 infection, suspected

COVID-19 infection, general circumstances around COVID-19 without infection or any other deviation from the protocol due to COVID-19.

Summary and listing (see Section 5.1.3) to describe the impact due to COVID-19 will be performed.

Summary and listing to describe the AE related to COVID-19 vaccination will be provided (see Section 10.2.1)

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The subject randomization for this study is stratified by

- country, and
- LEV use (LEV naïve versus prior LEV use), and
- number of prior AEDs (≤2 versus >2) based on AEDs previously used and discontinued prior to Visit 1.

In this regard, the primary analyses based on ANCOVA will include an effect for treatment, an effect for country, and an effect for the 4 combinations of levels for LEV status and number of previous AEDs. The actual stratification level (see Section 3.2.4) will be used for the primary analyses. Lower-enrolling countries will be pooled as described below.

The primary analyses will also adjust for log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate. The adjustment for this covariate will account for any imbalance across treatment groups with respect to Baseline partial seizure frequency.

To minimize the risk of issues due to data sparsity, any country with fewer than 20 subjects in the FAS population will be pooled with an appropriately selected country. Based on the number of enrolled subjects, it is concluded Taiwan, Singapore, and Malaysia will be combined together due to small number of participants in each country.

4.2 Handling of dropouts or missing data

Seizure frequency will be computed over non-missing days in the DRC as described in Section 3.9.3; missing seizure days in the DRC will not be considered in the calculation of seizure frequency. Generally, compliance with the DRC is expected to be high in a refractory population and, therefore, the impact of missing data in the DRC is expected to be minimal. However, the impact of missing data of DRC cannot be ruled out, and missing data will be assessed as part of the DEM prior to database lock to ensure an acceptable level of compliance with the seizure data in the DRC across the study population.

For subjects who prematurely discontinue during the Treatment Period, the calculation of 28-day adjusted partial seizure frequency over the Treatment Period will be based on available seizure data in the DRC up to the time of last visit during the Treatment Period. This effectively imputes the unobserved seizure frequency after discontinuation with the seizure frequency observed prior to discontinuation. The potential impact of dropouts cannot be ignored; however, a low percentage of dropouts has generally been observed across BRV treatment groups in prior

studies of similar design for BRV with no clear dose-response with regard to either overall dropout rate or rate of dropout due to AEs.

4.3 Interim analyses and data monitoring

No formal interim analyses are planned for this study. Regular monitoring of safety data collected during clinical studies will be performed by medically qualified Sponsor personnel or equivalent designee(s).

4.4 Multicenter studies

Study outcomes will not be assessed for individual investigator sites due to the expected low enrollment within each investigator site and because the subject randomization is not stratified by investigator site. Treatment by investigator site interactions will not be assessed.

4.5 Multiple comparisons/multiplicity

This study can be considered positive if superiority of at least 1 of 2 active treatment groups to a control treatment group is demonstrated for a primary efficacy variable. It indicates that multiplicity of multiple comparisons of treatment groups should be controlled critically.

Statistical testing will be based on the comparison of each BRV treatment group (BRV 50mg/day and 200mg/day) to PBO with control of overall type I error rate based on the Hochberg procedure. The Hochberg procedure does not require a pre-specified order of testing for BRV treatment groups versus PBO. In a setting with a comparison of 2 active treatment groups to PBO, the Hochberg procedure is applied by first testing the BRV treatment group with the larger 2-sided p-value at 0.05 level. If statistical significance is achieved at this step, then the study is positive and both BRV treatment groups are declared statistically different from PBO. If the largest p-value is not significant at the 0.05 level, then the Hochberg procedure steps to the smaller p-value and tests at 0.025 level. If statistical significance is achieved at this step, then the study is positive and the BRV treatment group associated with the smaller p-value is declared statistically different from PBO. If the smaller p-value is not significant at the 0.025 level, then neither BRV treatment group is statistically different from PBO nor is the study positive.

	Significant level	Unadjusted p-value	Adjusted p-value
Step 1	0.05	p_1 (larger one)	p_1
Step 2	0.025 (=0.05/2)	p_2 ($<p_1$)	min (p_1, $p_2 \times 2$)

4.6 Active-control studies intended to show equivalence

Efficacy outcomes are based on superiority comparisons of each BRV treatment group to PBO; this section is therefore not applicable for this study.

4.7 Examination of subgroups

Subgroup analysis will be conducted for the following efficacy outcomes:

- Percent reduction in partial seizure frequency (per 28 days during the 12-week Treatment Period) over PBO based on ANCOVA

- 50% responder rate based on percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period
- Percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

The above selected efficacy outcomes will be evaluated for the following subgroup variables:

- Gender
- Categorized age (<17 years, 17 to <65 years, 65 years and older)
- Country (Japan, China Mainland, Philippines, Thailand, Taiwan, Singapore, and Malaysia, where Taiwan, Singapore, and Malaysia will be combined together due to small number of participants in each country, see Section 4.1)
- Region (Japan, non-Japan)
- LEV use (LEV naive, prior LEV use) according to actual stratification level as per the CRF
- Number of AEDs previously used but discontinued prior to study entry (≤2 versus >2) according to actual stratification level as per the CRF
- AED inducer status (use of an inducer at study entry versus no inducer at study entry)

  The AED inducer will be captured according to the drug list provided by UCB.
- Seizure type at Baseline (types IA, IB, and IC)

  Subjects who experience at least one type of IA, IB, and IC seizure, respectively, during the Baseline Period will be included in the analysis for that seizure type. Subjects may be classified into more than 1 subgroup based on their baseline seizure profile.

All evaluations will be descriptive; neither statistical testing of treatment by subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

5.1.1 Overall subject disposition

Subjects will be allowed for rescreening if he or she failed the eligibility criteria at his/her first screening attempt. The number of screening events, screened subjects, number of screen failures and the primary reason for screen failure, number of rescreened and failed again and the primary reason for rescreening failure, and overall successfully screened subjects will be summarized for the ES.

The overall summary of disposition for the RS will present the number and percentage of subjects for the categories described below. A patient will be regarded as completing a study period if he or she completed the last scheduled visit within the study period. All percentages will be relative to the number of subjects in the RS.

Overall Disposition

- The number of subjects completing the double-blind part of the study (ie, the Treatment Period, the Down-Titration Period, Study Drug Free Period and the Transition Period)
- The number of subjects discontinuing double-blind part of the study and the primary reason for discontinuation

Treatment Period Disposition

- The number of subjects completing the Treatment Period
  - The number of subjects completing the Treatment Period and entering the Down-Titration Period
  - The number of subjects completing the Treatment Period and entering the Transition Period
- The number of subjects discontinuing during the Treatment Period and the primary reason for discontinuation
  - The number of subjects discontinuing during the Treatment Period and entering the Down-Titration Period
  - The number of subjects discontinuing during the Treatment Period and not entering the Down-Titration Period

Down-Titration Period Disposition

- The number of subjects entering the Down-Titration Period
- The number of subjects completing the Down-Titration Period

A subject is considered completing the Down-Titration Period if this subject also completes the Study Drug Free Period.

- The number of subjects discontinuing the Down-Titration Period and the primary reason for discontinuation

Transition Period Disposition

- The number of subjects entering the Transition Period
- The number of subjects completed the Transition Period and transited to LTFU or MAP
- The number of subjects discontinuing during the Transition Period and not entering the LTFU or MAP and the primary reason for discontinuation

Open-Label Temporary Period Disposition

- The number of subjects entering the Open-Label Temporary Period
- The number of subjects discontinuing during the Open-Label Temporary Period and the primary reason for discontinuation

Open-Label Temporary Period and MAP are not applicable to subjects enrolled in Japan and China. Percentages for Open-Label Temporary Period will be relative to the number of subjects entering the Open-Label Period in the RS.

In addition to the overall summary of disposition, the above will also be summarized by LEV status, and number of previous AEDs (≤2 versus >2) according to the actual stratification level as per the CRF.

In order to meet the EudraCT reporting requirement, a summary table of discontinuation due to AEs will be provided.

Subject disposition will be listed for all subjects screened and will include the following information: subject status (screen failure, completed or dropout), date of informed consent, date of randomization, dates of first and last dose of study medication, total days on study medication, and the date of final contact for the subject. Further discontinuation information will be listed for all subjects discontinued from the study including primary reason for discontinuation, period in which subjects discontinued, and dose as well as days on dose from which the subject discontinued. The listing will also include the date and reason for breaking the randomization code (if applicable). For screen failures the date and reason for screen failure will be listed instead of the last dose of study medication and the primary reason for discontinuation, respectively, for discontinued subjects.

A subject data listing for rescreened subjects will also be prepared including previously assigned subject number, final subject number, screening status, date of informed consent, date of screen failure and reason for screen failure.

5.1.2 Disposition by investigator site

An overview of the date of first subject in (earliest Visit 1), date of last subject out (latest scheduled or unscheduled visit), and the number of screened subjects will be summarized for all study sites, individual study site and country. Additionally, the number of randomized subjects and the number of subjects in each of the SS, FAS, PK-PPS and PPS will be summarized for all treatment groups combined and by treatment group for all study sites, study site and for country.

5.1.3 Number of subjects completing each visit

The number and percentage of randomized subjects completing each scheduled visit will be summarized for the RS. EDVs that correspond to scheduled visits will be included in the counts for the scheduled visits to which they correspond. EDVs occurred before Visit 7 will be re-mapped to the next scheduled visit.

A subject data listing including treatment group, study period, visit number, visit label, visit date, and relative day will be prepared for the RS.

A separate table presenting the impact of COVID-19 for any reason will be summarized by impact category and timepoint (visits and non-visit events) for all randomized subjects. Subject will be counted more than once if the subject has multiple impact categories at each timepoint.

A subject data listing including visit, date, relationship to COVID-19, impact category and narrative of event will be presented for the RS.

5.1.4 Number of subjects by stratification levels

The number and percentage of randomized subjects for each level of LEV status (never used LEV versus prior LEV use only), and number of AEDs previously used but discontinued prior to study entry (≤2 versus >2) will be summarized overall per the data entered in IVRS system and per the actual levels according to the CRF data, separately.

The number and percentage of randomized subjects with discrepancies between the IVRS stratification and the actual stratification levels identified on the CRF will be summarized for LEV status and number of previous AEDs.

Additionally, the number and percentage of randomized subjects by country will be summarized.

5.2 Important protocol deviations

The number and percentage of randomized subjects with at least 1 IPD will be summarized overall and by main category of protocol deviation for randomized subjects. Specific categories of protocol deviations will be defined within the IPD.

The assignment of subjects to each of the analysis sets will be listed for the ES. In addition, IPDs will be listed as well as whether it excluded the subject from the per-protocol analysis based on the RS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized by treatment group, over all subjects on BRV treatment and over all subjects. Unless otherwise specified, tables will be provided for the FAS and listings will be done for the ES.

6.1 Demographics

Age in years will be calculated based on date of informed consent and an incomplete birth date assuming birth on the first day of the month (yyyy-mm-01). Weight will be summarized at Visit 1 and body mass index (BMI) will be calculated using the following formula with the subject weight recorded at Visit 1.

$$\text{BMI } (\text{kg/m}^2) = \text{weight (kg)} / \text{height}^2 \text{ (m)}$$

Tables with descriptive statistics for the FAS as well as the SS and listings for the ES will be given for the demographic variables: age, categorized age [(the standard for BRV adult studies; <17, 17 to <65, and ≥65 years) (EudraCT; 12 to <18, 18 to <65, 65 to <85, and ≥85 years) and (clinicaltrials.gov; ≤18, 19 to <65 and ≥65 years)], gender, race (ie, racial group) , ethnicity, ethnic subgroup, countries, height, weight, BMI, categorized BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40), and AED inducer status.

No tables will be presented for childbearing potential/birth control. A subject data listing will cover gender, subject of childbearing potential/fertile (yes/no), method of birth control, and reason not of child-bearing potential/fertile.

6.2 Other Baseline characteristics

6.2.1 Epileptic seizure profile

The number and percentage of subjects experiencing each seizure type at any time prior to study entry will be summarized based on the ILAE classification (1981) (see protocol Appendix).

The overall number and percentage of subjects with a history of type I, II and III seizures will be summarized with their subclasses. A subject will be classified as having a history of type I seizures if the subject has a history of IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, or IC seizures. A subject will be classified as having a history of type II seizures if the subject has a history of IIA,

IIB, IIC, IID, IIE, or IIF seizures. A listing will include the historical seizure types based on the ILAE classification.

6.2.2 Classification of epileptic syndrome

Classification of epileptic syndrome will be summarized based on the classifications of epilepsy and epileptic syndrome (ILAE, 1989) (see protocol Appendix). An appropriate listing will be done.

6.2.3 History of epileptic seizures

History of epileptic seizures will summarize whether history or presence of status epilepticus during the year preceding Visit 1 or during Baseline Period, whether at least 2 partial seizures per month were experienced during the 3 months before Visit 1, epilepsy duration in years, age at time of first seizure in years, and percent of life with epilepsy. A listing reflecting epilepsy duration in years, age at time of first seizure in years, and percent of life with epilepsy will be provided in addition.

Epilepsy Duration

Epilepsy duration is the number of years from the first date of diagnosis of epilepsy to the date of informed consent.

The epilepsy duration (years) will be derived as the date of informed consent minus the date of the first diagnosis (yyyy-mm-01), which is similar to the derivation of age. For subjects who only have a year of the diagnosis date, the date of January 1 will be assumed. If an imputed date of the diagnosis is less than the date of birth due to the application of imputation rules, then set epilepsy duration equal to the subject's age. No imputation will be done for completely missing diagnosis date and epilepsy duration will not be calculated for subjects with completely missing diagnosis date.

Age at Time of First Seizure

Calculated in the same manner as age, but using the date of first diagnosis of epilepsy in place of the date of informed consent.

For partial dates of birth and first diagnosis of epilepsy, imputation rules are applied. If an imputed date of first diagnosis of epilepsy is less than the date of birth due to the application of imputation rules, then set the date of first diagnosis of epilepsy to the date of birth. For completely missing dates of first diagnosis of epilepsy, no imputation will be done and age at time of first seizure will not be calculated.

Percent of Life with Epilepsy

Percent of life with epilepsy will be calculated as 100 times epilepsy duration divided by the subject's age which is calculated based on date of informed consent. Based on defined rules it should not be possible to have a calculated percent of life with epilepsy that is either <0% or >100%.

6.2.4 Seizure types and frequency experienced during Baseline

The number and percentage of subjects who experienced each seizure type during the Baseline Period will be presented for FAS in the same way as epileptic seizure profile in the Section 6.2.1.

In addition, baseline partial seizure frequency will be summarized descriptively for subjects who experienced at least one seizure of type I (IA, IB or IC) during the Baseline Period using FAS. Summaries will be presented for separate types IA, IB, IC and for overall type I.

6.3 Medical history and procedures

6.3.1 Previous and ongoing medical history

The number and percentage of subjects with a medical history condition, including both resolved and ongoing conditions at the time of study entry, will be summarized overall and by MedDRA primary system organ class (SOC) and preferred term (PT) according to the SS. A listing of subjects with previous and ongoing medical history will be provided. A separate listing of medical history glossary which represent mapping of reported terms to PTs and SOCs based on the MedDRA coding dictionary will also be provided.

6.3.2 Procedure history and concomitant medical procedures

Listings of subjects with procedure history for the ES and concomitant medical procedures in the RS will be provided, separately.

6.4 History of previous AED use

Previous AEDs are AEDs taken and discontinued prior to study entry. The history of previous AED will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol. However, investigator's judgement will be prioritized and taken into consideration. Summaries in this section will be based on the History of Previous AED Treatment CRF which includes only AEDs stopped prior to study entry.

For summaries by preferred drug name, some AEDs will be grouped as follows (same grouping rules in Section 3.2.4):

Valproate includes valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, ergenyl chrono, valproic acid.

Phenytoin includes phenytoin sodium, phenytoin calcium, mephenytoin, zentronal, metetoin, ethotoin, albutoin, hydantal, phelantin, hydantol D, anirrit, dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, hydantoin.

Phenobarbital includes phenobarbital sodium, methylphenobarbital, metharbital, alepsal, phenobarbital, kaneuron, epanal.

Benzodiazepine AEDs are grouped separately by bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate.

Other combination AEDs are not considered for grouping.

In addition to the following summary tables, a corresponding subject data listing will be provided.

6.4.1 Number of previous AEDs

The number of previous AEDs will be summarized based on the following categorization: 0-1, 2-4, and ≥5 AEDs. When counting the number of previous AED from the CRF form "History of Previous Antiepileptic Drug Treatment", if the same compound name is also entered in the CRF

form “Prior and Concomitant Medications”, the drug is not counted as a previous AED (see Section 3.2.4).

6.4.2 History of previous AEDs

The number and percentage of subjects who had taken at least 1 AED prior to study entry will be summarized overall and by preferred drug name.

6.4.3 Previous AEDs by reason for AED discontinuation

The number and percentage of subjects by reason for discontinuation of previous AEDs (insufficient efficacy, adverse drug reaction, tachyphylaxis, remission, other, unknown) will be summarized. Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.

6.4.4 LEV status

LEV status (LEV naïve or prior LEV use) will be summarized. Subject is considered LEV naïve if he/she has never taken LEV. Prior LEV use means the subject has taken LEV at any time prior to Visit 1 and discontinued prior to Visit 1.

6.5 Concomitant medications

Summaries in this section will be based on the CRF form “Prior and Concomitant Medications (including AEDs)”. In addition to the following summary tables, a corresponding subject data listing will be provided with a glossary of medications which represents mapping of reported terms to WHO DRL pharmacological group and preferred drug name. The glossary list will cover medications found not only in prior and concomitant medications but also in previous AEDs.

Prior medication is defined as any medication (including AEDs) with end date prior to the first administration of study medication.

Concomitant AEDs (including AEDs taken at study entry) will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol and will be captured according to the CRF “Core AED?” based on the investigator’s judgement.

Medications taken at study entry are the ongoing medications at the study entry (Visit 1).

6.5.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AED medications at the time of study entry will be summarized by WHO-DRL pharmacological group and preferred drug name according to the SS.

6.5.2 Number of AEDs taken at study entry

The number and percentage of subjects taking 1, 2, and ≥3 AEDs at the time of study entry will be summarized overall and separately by VNS status at study entry (no VNS or VNS not active versus currently active VNS).

6.5.3 AEDs taken at study entry

AEDs taken at the time of study entry will be summarized by WHO-DRL preferred drug name. The AEDs will be grouped in the same way as indicated in Section 6.4.

6.5.4 Concomitant AEDs

Concomitant AEDs are AEDs that were taken during the study on/after the first dose of IMP, regardless of the start and stop date of the AED. The number and percentage of subjects taking concomitant AEDs will be summarized by WHO-DRL preferred drug name.

6.5.5 Use of vagal nerve stimulation at study entry

Use of vagal nerve stimulation (VNS) will be identified from the VNS Status at Baseline CRF module. The number and percentage of subjects with an active VNS and the number and percentage of subjects with no VNS implant or a non-active VNS implant will be summarized.

All other VNS data at study entry (eg, VNS settings) will be provided in subject data listings.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

IMP compliance (%) will be calculated according to the definition shown in the formula below;

$$\text{Compliance}(\%) = 100 \times \frac{\text{Number of tablets taken}}{\text{Number of tablets that should have been taken}}$$

In general, for a duration where the number of tablets which should be taken per day is constant, the compliance is represented as follows;

$$\text{Compliance}(\%) = 100 \times \frac{(\text{Number of tablets dispensed}) - (\text{Number of tablets returned})}{(\text{Number of tablets per day}) \times (\text{Number of days in the duration})}$$

If a period where the number of tablets which should be taken per day may not be constant, the compliance will be calculated as a weighted sum of compliance of each duration weighted by length of the duration.

$$\text{Compliance}(\%) = 100 \times \sum_i (C_i \times W_i),$$

where i represents a duration with a constant number of tablets per day,

$$C_i = \frac{(\text{Number of tablets dispensed for } i)\text{-}(\text{Number of tablets returned for } i)}{(\text{Number of tablets per day for } i) \times [(\text{End date of } i) - (\text{Start date of } i)]},$$

$$W_i = \frac{(\text{End date of } i) - (\text{Start date of } i)}{(\text{End date of Period}) - (\text{Start date of Period})}.$$

Note that the first and last day of treatment are considered as half days because the start day of each duration will contribute evening only and the last day of it will contribute morning only.

For a period where treatment is double-blind, the number of tablets which should been taken per day is defined in Table 3.1, Table 3.2 and Table 3.3.

For instance, total planned tablet number during the Treatment Period will be calculated as 6 times the number of days from the first dose of IMP (Visit 3) up to the last visit in the period (EDV for early discontinuers, Visit 7 otherwise).

Compliance for Treatment Period (%)

$$= 100 \times \frac{\text{(Number of tablets dispensed)-(Number of tablets returned)}}{6 \times [\text{(Date of EDV or Visit 7)} - \text{(Date of Visit 3)}]}$$

For the overall compliance which consists of the Treatment Period and either the Transition Period or the Down-Titration Period, the denominator of the formula for W_i is represented as [(the latest date of EDV, Visit 7 and Visit 8) − (Date of Visit 3)].

For the Open-Label Temporary Period, C_i can be applied for the above formula as only BRV 25mg tablet will be used.

$$C_i = \frac{\text{(Number of tablets dispensed)-(Number of tablets returned)}}{\frac{\text{(Daily Dose)}}{25}} \times [\text{(End date of Visit } i) - \text{(Start date of Visit } i)]$$

Note that end date of visit *i* is the same as the start date of visit *i*+1.

Compliance will be summarized for the SS with quantitative descriptive statistics by treatment group and overall for the Treatment, Transition, Down-titration Periods and overall periods except Open-Label Temporary Period, which will be summarized separately only for the entire population. Additionally, the number and percentage of subjects with compliance levels <80%, 80% to 120%, and >120% will be summarized as well.

Compliance for each period will be listed for each subject.

8 EFFICACY ANALYSES

Unless otherwise indicated, all efficacy analyses will be carried out for the FAS.

Unless otherwise specified, statistical testing for supportive and secondary analyses will be carried out at a nominal two-sided 0.05 significance level without multiplicity adjustment.

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Primary efficacy variable

The primary efficacy variable is the partial seizure frequency per 28 days during the 12-week Treatment Period. The details regarding the calculation of standardized seizure frequencies are provided in Sections 3.9.1, 3.9.2, and 3.9.3.

8.1.2 Primary analysis of the primary efficacy variable

The primary efficacy outcome will be the percent reduction in partial seizure frequency per 28 days during the Treatment Period of each BRV treatment individually over PBO.

The primary analysis will be based on ANCOVA with log-transformed [log(*x*+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for treatment, an effect for country, and an effect for the 4 combinations of actual stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the CRF data (see Section 3.2.4), and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate. Lower enrolling countries will be pooled for this analysis as described in Section 4.1.

Statistical treatment group comparisons will be based on the comparison of each BRV treatment group to PBO on the log-transformed scale using the above ANCOVA model. The evaluation of statistical significance will be based on the Hochberg multiple comparison procedure as described in Section 4.5. Both multiplicity-adjusted and unadjusted p-values will be presented.

Treatment effects will be characterized using percent reduction over PBO based on back transformation of least squares (LS) means obtained for each treatment group from the above ANCOVA model. Percent reduction will be calculated using the following formula, where LS Mean (PBO) is the LS mean for the PBO treatment group and LS Mean (BRV) is the LS mean for either the BRV 50mg/day or BRV 200mg/day treatment group:

$$\%\,\text{Reduction / PBO} = 100 \times \frac{\exp[\text{LS Mean(PBO)}] - \exp[\text{LS Mean(BRV)}]}{\exp[\text{LS Mean(PBO)}]}$$

The following formula is equivalent to the above:

$$\%\,\text{Reduction / PBO} = 100 \times \left[1 - \exp[\text{LS Mean(BRV)} - \text{LS Mean(PBO)}]\right]$$

Two-sided 95% CIs for the comparison of each BRV treatment group to PBO will also be obtained using the above ANCOVA model. Confidence limits will be back-transformed using the above formula to obtain confidence limits for percent reduction over PBO. Confidence limits will not be adjusted for multiplicity and will correspond to a nominal two-sided 0.05 significance level.

During the conduct of the randomization, some subjects with the stratification levels mistakenly entered to the IVRS system and a sensitivity analysis will be performed to assess the impact due to this error. The sensitivity analysis will be conducted to the primary efficacy variable using the similar ANCOVA model with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for treatment, an effect for country, and an effect for the 4 combinations of stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the IVRS data, and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate.

8.1.3 Supportive analyses of the primary efficacy variable

8.1.3.1 Non-parametric analysis

A non-parametric ANCOVA will be carried out to assess the robustness of the parametric ANCOVA results. The following steps will be applied to perform this analysis:

1. Baseline and Treatment Period 28-day adjusted partial seizure frequency will each be ranked across subjects in the PBO and BRV 50mg/day treatment groups
2. A regression of ranked Treatment Period partial seizure frequency versus ranked Baseline partial seizure frequencies will be performed using the ranked values from Step 1
3. A Mantel-Haenszel test to assess difference in row-mean scores will be applied to the residuals from Step 2
4. The above steps will be repeated for the comparison of BRV 200mg/day versus PBO.

8.1.3.2 Per-protocol analysis

The primary efficacy variable will be analyzed for the PPS for the percent reduction over PBO based on ANCOVA as described in Section 8.1.2.

8.2 Statistical analysis of the secondary efficacy variable(s)

8.2.1 Percent reduction in partial seizure frequency

Percent reduction from Baseline to the Treatment Period in partial seizure frequency will be calculated by subtracting 28-day adjusted Treatment Period partial seizure frequency [A] from 28-day adjusted Baseline Period partial seizure frequency [B], and multiplying the resulting quantity by 100 and dividing by the Baseline Period 28-day adjusted partial seizure frequency.

$$\%\text{Reduction} = 100 \times \frac{[\text{B}] - [\text{A}]}{[\text{B}]}$$

Percent reduction in partial seizure frequency from Baseline to the Treatment Period as well as [A], [B] and [B]-[A] will be summarized with quantitative descriptive statistics. Statistical comparisons between each BRV treatment group and PBO will be based on a Wilcoxon-Mann-Whitney test. Hodges-Lehmann non-parametric effect estimates and corresponding two-sided 95% CIs will be provided for the effect difference between each BRV treatment group versus PBO.

Plots displaying the complementary cumulative distribution function for percent reduction from Baseline to the Treatment Period will be provided.

8.2.2 50% responder rate in partial seizure frequency

The 50% responder outcome will be evaluated based on percent reduction in partial seizure frequency per 28 days from Baseline to the Treatment Period. A subject with at least a 50% reduction in 28-day adjusted partial seizure frequency is classified as a responder.

$$50\%\ \text{Responder Rate}\ (\%) = \frac{\text{Number of 50\% responders}}{\text{Number of subjects in the analysis set}} \times 100$$

The number and rate (%) of the responders for each treatment group will be summarized with the corresponding 95% CI for the rate. The CIs will be calculated by an exact method for the binomial distribution (ie, Clopper-Pearson interval).

Statistical comparisons between each BRV treatment group and PBO will be conducted with logistic regression (based on Firth's penalized maximum likelihood inferences). The logistic regression analysis will be done for the event (50% reduction or more) with the predictors described in Section 8.1.2. If the model does not converge or does not produce the estimates, the covariates may be modified. An odds ratio of BRV/PBO for each BRV treatment group will be estimated with its profile-likelihood 95% CI. Both multiplicity-adjusted and unadjusted p-values for the Wald chi-square test for treatment effect will be given.

In addition, 50% responder outcome will be evaluated for the PPS as described above.

8.2.3 Categorized percent reduction in partial seizure frequency

The number and percentage of subjects within each of the following categories of percent reduction in partial seizure frequency from Baseline to the Treatment Period will be summarized

for each treatment group: <-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%. Statistical comparisons between each BRV treatment group and PBO will be based on a Mantel-Haenszel test for the comparison of row mean scores.

8.2.4 Seizure freedom (partial, all epileptic seizure)

Seizure freedom will be assessed separately for partial seizure and for all epileptic seizure.

A subject is defined as all epileptic seizure free over the Treatment Period if they meet all of the following criteria.

1. The subject completed the Treatment Period
2. The subject did not have any missing days in the DRC during the Treatment Period, and
3. The subject did not report any seizures during the Treatment Period

The algorithm rules for all epileptic seizure freedom are described in Section 3.9.4.1.

The number and percentage of subjects who are seizure free for partial seizure and for all seizure types over the Treatment Period will be summarized.

Additionally, the number and percentage of subjects who met each individual criterion will be summarized, irrespective of whether the other criteria were met. Furthermore, the number and percentage of subjects meeting criteria 2 and 3 but not meeting criterion 1 (ie, subjects without seizures and without missing days in the DRC but discontinued) will be summarized.

Seizure freedom rates for all seizure types will be compared between each BRV treatment group and PBO using Fisher's Exact Test.

The analysis above will be repeated for partial seizure instead of all epileptic seizure (also refer to Section 3.9.4.2).

8.2.5 Seizure frequency for all seizure types

Estimates of percent reduction over PBO and odds ratios for 50% responder rates and corresponding two-sided 95% CIs for seizure frequency for all seizure types (I+II+III) will be provided based on the statistical methodology described in Section 8.1.1, Section 8.1.2 and Section 8.2.2. Additionally, percent reduction from Baseline in seizure frequency for all seizure types will be analyzed as described in Section 8.2.1. Statistical treatment group comparisons will also be provided as described in these sections. In addition, seizure frequency will be listed by subject, study period and seizure type. The data from the DRC will also be listed by subject and study period.

8.2.6 Time to n^{th} partial seizure

The algorithm rules for time to n^{th} partial seizure are described in Section 3.9.5.

Median time to n^{th} seizure and corresponding 95% CIs will be provided based on Kaplan–Meier (KM) estimation. KM plots will be provided for time to n^{th} partial seizure (n=1, 5, 10).

Time to n^{th} partial seizure will be compared between each BRV treatment group and PBO using a semi-parametric proportional hazards regression model with an effect for country, an effect for the 4 combinations of actual stratification levels for LEV status and number of previous AEDs (≤2 versus >2) per the CRF data, and log-transformed Baseline partial seizure frequency as a continuous covariate. Significance probabilities (ie, p-values) and hazard ratios and

corresponding two-sided 95% CIs will be presented for the comparison of each BRV treatment group to PBO. Lower enrolling countries will be pooled for this analysis as described in Section 4.1.

9 PHARMACOKINETICS

In addition to the following analyses for PK, population PK and/or PK/PD analyses will be considered as needed and described in a separate data analysis plan.

9.1 BRV plasma concentrations

The daily dose information for PK analysis will be calculated according to the "Last Dosage Amount" from the CRF form: "BRV Plasma Level Monitoring":

- If the last dosage amount is 25mg/dose, the total daily dose will be 50mg/day
- If the last dosage amount is 100mg/dose, the total daily dose will be 200mg/day
- In case the subjects enter the Transition Period (Visit 8), the last dosage amount can be 75mg/day and the total daily dose will be 150mg/day.

Descriptive statistics in Section 3.1.1 for BRV observed plasma concentrations are computed per defined time window post-dose (>0-4 hours, >4-8 hours, and >8 hours, based on the date and time of last intake of IMP prior to blood sampling) for all PK-PPS by actual dose given before each blood sampling for PK and dose normalized BRV plasma concentrations are computed for all doses with the same manner. 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 BRV observed concentrations versus median time are presented by actual dose given before each blood sampling for PK and by visit. Median time will be calculated separately by each time window post-dose (>0-4 hours, >4-8 hours, and >8 hours). Daily dose normalized (to 50mg) BRV plasma concentrations will be presented with the same manner.

Figures of individual observed BRV plasma concentrations versus time after the last intake of IMP prior to blood sampling will be presented by actual dose given before each blood sampling for PK and by visit. Dose normalized (to 50mg) BRV plasma concentrations will be presented with the same manner.

Furthermore, above analyses are repeated for Japanese and Non-Japanese.

A subject data listing of BRV Plasma Concentration Monitoring covers

- Treatment Group
- Site-Subject Number
- Gender/Age(years)/Race/Weight(kg)
- Visit
- Not Done (with a flag 'ND')
- Last dose of study medication prior to Blood Sampling: (Datetime) (yyyy-mm-ddThh:mm)/Relative Day

- Blood Sampling Datetime (yyyy-mm-ddThh:mm:ss)/Relative Hours to Last Medication
- Last Dose (mg/day)
- Plasma BRV Concentration (µg/mL)
- Time Window [>0-4 hours, >4-8 hours, and >8 hours post dosing]
- Dose Normalized Plasma Level (µg/mL/50mg): equivalent to 50mg/day

10 SAFETY ANALYSES

Safety is assessed with AEs, laboratory tests (blood chemistry, hematology, urinalysis, and pregnancy test), vital signs, body weight, ECGs, physical examination, neurological examination, mental status, and psychiatric status. Summary tables will be provided for AEs; blood chemistry, hematology, and urinalysis; vital signs; body weight; and ECGs. No summary tables will be provided for pregnancy testing, physical examination, neurological examination, mental status, or psychiatric status.

All safety summaries will be based on the SS.

Regarding safety for the Open-Label Temporary Period, it will be summarized separately from other preceding study periods as described in Section 3.2.2.

10.1 Extent of exposure

The duration of study medication exposure for the Treatment Period will be calculated as the date of last dose of IMP during the Treatment Period minus the date of first dose of IMP plus 1 day. The overall duration of study medication exposure for the entire study will be calculated as the date of last dose of IMP minus the date of first dose of IMP plus 1 day.

The duration of study medication exposure and the overall duration of IMP exposure will be summarized with quantitative descriptive statistics for the Treatment Period and for the entire study (except the Open-Label Temporary Period), respectively, for the SS. The number and percentage of subjects with the following categories of durations of study medication exposure for the Treatment Period and the entire study will also be summarized:>0 weeks, >=2 weeks, >=4 weeks, >=6 weeks, >=8 weeks, >=10 weeks, and >=12 weeks.

10.2 Adverse events

TEAEs are defined as AEs which had onset on or after the first dose of IMP. AEs with an incomplete onset date will be classified as TEAEs if the month and year of onset (when only the month and year are specified) is the same as or after the month and year of the first dose of IMP or the year of onset (when only year is specified) is the same as or after the year of first dose of IMP.

AEs are classified by study period as described in Section 3.2.2.

10.2.1 General summaries of AEs

An overall summary of TEAEs will provide the overall number of TEAEs and the numbers and percentages of subjects with at least 1 TEAE, with a TEAE that led to permanent discontinuation of study drug, with a TEAE leading to withdrawal from study, with a TEAE requiring dose change, with a drug-related TEAE, with a severe TEAE, and with a treatment-emergent serious

AE (SAE). The number and percentage of subjects who died due to AE as well as TEAE will also be summarized.

The following summaries of TEAEs will be provided by primary SOC and PT. All summaries are for all study periods combined excluding Open-Label Temporary period (Treatment, Down-Titration, Study Drug-Free Period, and Transition) unless otherwise indicated. Summaries for Open-Label Temporary will be presented separately. The number of individual occurrences will be included with the numbers and percentages if applicable.

- Incidence of TEAEs
- Incidence of TEAEs by study period (Treatment, Down-Titration, Study Drug-Free, and Transition Periods)
- Incidence of drug-related TEAEs by study period (Treatment, Down-Titration, Study Drug-Free, and Transition Periods)
- Incidence of TEAEs occurring in at least 2% of subjects in any treatment group
- Incidence of TEAEs occurring in at least 2% of subjects by relationship to study drug in any treatment group
- Incidence of non-serious TEAEs occurring in at least 5% of subjects in any treatment group
- Incidence of non-serious TEAEs occurring in at least 5% of subjects by relationship to study drug in any treatment group
- Incidence of TEAEs by intensity
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs by relationship to study drug
- Incidence of TEAEs by maximum relationship to study drug
- Incidence of treatment-emergent SAEs
- Incidence of non-serious TEAEs
- Incidence of TEAEs leading to permanent discontinuation of study drug
- Incidence of TEAEs leading to discontinuation of study
- Incidence of TEAEs related to COVID-19 vaccination by study period

For the summary by maximum intensity and by maximum relationship, each subject will be counted at most once per primary SOC or PT according to the maximum intensity and the maximum relationship of all AEs within that SOC or PT. For the summary by intensity and by relationship, a subject may be counted more than once according to the intensity of the TEAEs and the relationship assessments.

Severe intensity will be assumed for AEs for which intensity is not specified.

Drug-related TEAEs are TEAEs for which the relationship to IMP is specified as Related or AEs for which relationship is not specified.

In addition, AEs including Pre-treatment AEs will be listed with respect to general information, relationship, seriousness, withdrawal of study drug and study discontinuation.

10.2.2 TEAEs of special interest

The following TEAEs are considered as TEAEs of special interest:

- autoimmune nephritis
- nephritis
- nephritis allergic
- tubulointerstitial nephritis
- uveitis syndrome
- potential Hy's law

The TEAEs of special interest, which are captured on the CRF page, will be categorized and presented by SOC, PT and relationship similar to appropriate description in Section 10.2.1.

10.3 Clinical laboratory evaluations

End of Treatment is defined as the last assessment point at which a measured value of the parameter is available during the Treatment Period regardless of scheduled visit or unscheduled visit. The same definition applies hereafter.

10.3.1 Hematology, Biochemistry and Urinalysis parameters

Hematology, biochemistry, and urinalysis parameters are assessed at Visits 1, 3 through 7, EDV, Visit 8, and the Safety Visit and may also be assessed at unscheduled visits.

Observed results as well as change from baseline will be analyzed descriptively for all laboratory parameters by visit and End of Treatment. Incidence of possibly clinically significant treatment-emergent (PCST) results, PCST low value, and PCST high value will be summarized for hematology, blood chemistry and urinalysis parameters, if applicable. The PCST criteria are defined in Section 12.2.1.

A serum pregnancy test is performed at Visit 1 and a urine pregnancy test is performed at Visit 2 and Visit 7/EDV. A urine pregnancy test may also be performed at unscheduled visits. Pregnancy test results will not be summarized but will be provided in a subject data listing.

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

10.3.2 PDILI laboratory measurements

The number and percentage of subjects with PDILI will be summarized by treatment group. The number and percentage of subjects meeting ALT or AST or both, total bilirubin, alkaline phosphatase criteria and presence of symptoms will be summarized in table.

Listings of subjects with PDILI include alcohol and illicit drug use within past 6 months, the laboratory results for ALT, AST and Total bilirubin, symptoms of hepatitis or hypersensitivity will be provided.

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

10.4.1 Vital signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate are assessed for Visits 1 through 7, EDV, Visit 8, and the Safety Visit and may also be assessed at unscheduled visits. Body weight is assessed at all of the same time points except for Visit 2.

Observed values for SBP, DBP, and pulse rate will be summarized for Visits 1 through 7, End of Treatment, Visit 8, and the Safety Visit. Changes from Baseline for SBP, DBP, and pulse rate will be summarized for Visits 4 through 7, End of Treatment, the Visit 8, and the Safety Visit. Same summaries will be provided for body weight.

The number and percentage of subjects with at least one PCST low values, and subjects with at least one PCST high value will be summarized for SBP, DBP, pulse rate, and body weight. Percentages will be relative to the number of subjects with an assessment within each study period. PCST criteria are defined in Section 12.2.2.

Vital signs measurements (absolute values and changes from Baseline) will be listed by visit and timing relative to dosing including changes from Baseline.

10.4.2 Electrocardiograms

ECGs are performed at Visits 1, 4, 5, 7/EDV and Visit 8, and may also be performed at unscheduled visits. An ECG is also performed at the Safety Visit if there is an abnormal finding at Visit 7/EDV.

As for the reported ECG parameters, the observed values and change from baseline will be presented descriptively by treatment group for each scheduled visit and End of Treatment.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding will be summarized for Visits 1, 4, 5, and 7; End of Treatment; Visit 8 (by Period) and the Safety Visit. Percentages will be relative to the number of subjects with an ECG at each analytical time point. Subjects will be counted at most once within each time point based on the worst observed outcome across all abnormalities at that time point.

Summaries of shift from Baseline to Visits 4, 5, and 7 and End of Treatment will also be provided based on the categories normal and abnormal.

Abnormal ECGs will be listed by subject, visit, and timing relative to dosing.

10.4.3 Electroencephalography

Electroencephalography (EEG) is performed at Visit 1 and appropriate data will only be listed by subject.

10.4.4 Computed tomography/ Magnetic resonance imaging

Computed tomography (CT) scan/ magnetic resonance imaging (MRI) is performed at Visit 1 and will be listed by subject and type of image.

10.4.5 Physical examination

A physical examination is performed at Visits 1, 3, and 7/EDV, Visit 8 and the Safety Visit and may also be performed at unscheduled visits, although findings are only recorded on the CRF at Visit 1. A listing of abnormal physical examination findings at Visit 1 will be provided; no summaries of physical examination findings are planned.

10.4.6 Neurological examination

A neurological examination is performed at Visits 1, 3, and 7/EDV, Visit 8 and at the Safety Visit and may also be performed at unscheduled visits. A listing of neurological examination results will be provided; no summaries of neurological examination findings are planned.

10.4.7 Psychiatric and mental status

An evaluation of Psychiatric and Mental Status is performed at Visits 1, 3, and 7/EDV, Visit 8 and at the Safety Visit and may also be performed at unscheduled visits. A listing of Psychiatric and Mental Status results will be provided; no summaries of Psychiatric and Mental Status findings are planned.

10.4.8 Columbia-Suicide Severity Rating Scale

With global amendment 1 to the protocol, the Columbia-Suicide Severity Rating Scale (C-SSRS) has been added as an assessment at all study visits to assess suicidality. Specific rules are provided to the study sites with regard to the identification of AEs or SAEs based on the outcome of this assessment. Because clinical events of interest will be recorded as AEs or SAEs, no study variable is defined for this assessment and no analyses are planned for the C-SSRS within the context of this study. However, subject data listings of the data for the C-SSRS will be provided.

11 REFERENCES

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988, 75: 800-2.

12 APPENDICES

12.1 Actual BRV dose conversion table

Table 12.1: Conversion from blinded daily dose to unblinded BRV daily dose

		Blinded Nominal Dose (mg/day) from Dosing Log CRF										
Treatment group	**Period or Visit**	**0**	**25**	**50**	**75**	**100**	**125**	**150**	**175**	**200**	**225**	**250**
200mg/day	Start day of Treatment Period	0	0	50	50	100	100					
	Treatment Period (except first and last dates)	0	0	*50*	50	*100*	100	*150*	150	*200*	200	200
	Day of end Treatment and start Transition	0	*25*	*50*	*75*	*100*	*125*	*150*	*175*	175		
	Transition Period (except first and last dates)	0	25	50	75	100	125	150				
	Last day of Transition Period	0	25	50	75							
50mg/day	Start day of Treatment Period	0	25	0	25	0	25					
	Treatment Period (except first and last dates)	0	25	*50*	25	*50*	25	*50*	25	*50*	25	50
	Day of end Treatment and start Transition	0	*25*	*50*	*25*	*50*	25	*50*	25	50		
	Transition Period	0	25	*50*	25	*50*	25	50				
	Last day of Transition Period	0	25	0	25							
PBO	Start day of Treatment Period	0	0	0	0	0	0					
	Treatment Period (except first and last dates)	0	0	0	0	0	0	0	0	0	0	0
	Day of end Treatment and start Transition	0	0	0	0	0	0	0	0	0		
	Transition Period (except first and last dates)	0	0	0	0	0	0	0				
	Last day of Transition Period	0	0	0	0							

Note: Figures in italics indicate that there are two theoretically possible doses, of which the higher one is selected.

12.2 PCST criteria

12.2.1 Laboratory assessments - PCST

The following criteria will be applied in the determination of PCST laboratory assessment values.

12.2.1.1 Hematology

Table 12–2: Hematology PCST criteria

PARAMETER	AGE RANGE	UNIT (standard)	ABNORMALITY CRITERIA (standard)
Hematocrit	<2y	%	≤27, >45
	2y - <18y		≤29, >47
	≥18y		≤85% of LLN, ≥115% of ULN
Hemoglobin	<2y	g/L	≤90, >150
	2y - <18y		≤95, >160
	≥18y		≤85% of LLN, ≥115% of ULN
WBC/Leukocytes	<12y	G/L	<3.5, >15.0
	≥12y		<3.0, >12.0
Neutrophils Absolute	>1m	G/L	<1.5
Lymphocytes	<6m	%	≤30.0
	6m - <6y		≤22.0
	6y - <18y		≤12.0, ≥80.0
	≥18y		≤10.0, ≥80.0
Basophils	>1m	%	≥3.0
Eosinophils	>1m	%	≥10.0
Monocytes	>1m	%	≥20.0
Platelets	>1m	G/L	≤100, >600
RBC/ Erythrocytes	<2y	T/L	<3.0
	≥2y		<3.5

Abbreviations: F=female; M=male; m=month; y= year. A month is defined as 30 days; a year is defined as 365.25 days.

12.2.1.2 Blood chemistry

Table 12–3: Chemistry PCST criteria

PARAMETER	AGE RANGE	UNIT (standard)	ABNORMALITY CRITERIA (standard)
AST (SGOT)	<14y	U/L	>180

PARAMETER	AGE RANGE	UNIT (standard)	ABNORMALITY CRITERIA (standard)
	≥14y		>144
ALT (SGPT)	1y - <18y	U/L	>90
	≥18y		>123
Alkaline Phosphatase	<4y	U/L	>690
	4y - <10y		>834
	10y - <18y		>1174
	≥18y		>432 (F), >933 (M)
GGT	<6m	U/L	>522
	6m - <1y		>279
	1y - <13y		>66
	13y - <18y		>126
	≥18y		>255
Total Bilirubin	>1m	umol/L	≥25.656
Total Protein	2m-<1y	g/L	<30, >100
	≥1y		<43, >100
Albumin	<1y	g/L	<16, >60
	≥1y		<24, >70
BUN	<1y	mmol/L	>7.497
	≥1y		>10.71
Urea	<1y	mmol/L	>7.014
	≥1y		>10.02
Creatinine	1y - <10y	umol/L	>79.56
	10y - <16y		>123.76
	≥16y		>141.44
Creatinine Clearance *	All	mL/s	<1.169
Calcium	<1y	mmol/L	<1.725, >3.05
	1y - <18y		<1.85, >2.925
	≥18y		≤1.975, ≥2.775
Phosphorous	<1y	mmol/L	<0.5814, >2.6486
	≥1y		<0.5814, >2.3902
Potassium	<1y	mmol/L	<3.0, >6.5

PARAMETER	AGE RANGE	UNIT (standard)	ABNORMALITY CRITERIA (standard)
	≥1y		<3.0, >5.8
Sodium	>1m	mmol/L	≤130, ≥150
Glucose	>1m	mmol/L	<2.775, >9.99
Total Cholesterol	1y - <18y	mmol/L	>6.475
	≥18y		>7.77
LDL (calculated)	1y - <18y	mmol/L	>3.626
	≥18y		>5.18
HDL	≤2y	mmol/L	<0.259
	>2y		<0.518
Triglycerides	<1y	mmol/L	>8.475
	≥1y		>2.825
Uric Acid	<1y	umol/L	>457.996
	1y - <13y		>386.62
	13y - <18y		>511.528
	≥18y		>404.464 (F), >571.008 (M)
Thyroxine (T4)	<1y	nmol/L	≤55.3453, ≥236.8264
	≥1y		≤48.9098, ≥173.7585
Globulin	<1y	g/L	<10, >38
	≥1y		<12, >44

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; F=female; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein; L = liter; M=male; m = month (a month is defined as 30 days) mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = years (a year is defined as 365.25 days)
* Schwartz equation (patients <12): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine; Cockroft equation (patients >12): Male: Cr Cl ml/min = [(140-age) × body weight (kg)] / (72 × serum creatinine); Female: Cr Cl ml/min = [(140-age) × body weight (kg)] / (72 × serum creatinine)] × 0.85

12.2.1.3 Urinalysis

[Instruction]

Qualitative urine parameters are generally reported by a descriptive score, which differs among laboratories. For data analysis purpose, a 4-point scale is used. Five-point, 6-point, or 7-point scales will be collapsed into a 4-point scale first. A value is considered possibly clinically significant treatment-emergent abnormal if an upward shift of at least 2 degrees from the baseline occurs under investigational treatment. To collapse the results in a 5-point scale into a 4-point scale, the lowest 2 positive results will be combined (see example below). For results

reported with a scale of more than 5-point, please consult your study physician for how to collapse into 4-point scale.

Original 5-point Scale	4-point Scale
Negative/None	Negative/None
Trace/Rare/Mild/A Few	Trace/1+/Rare/Mild/A Few
1+	
2+/Mod	2+/Mod
3+/Sev	3+/Sev

[Application]

Table 12–4: Urinalysis 4-point scales for PCST criteria

PARAMETER	Original Scale	4-point Scale for PCST
Protein	Negative, Trace, 30mg/dL, 100mg/dL, ≥300mg/dL, ≥1000mg/dL	Negative, (Trace, 30mg/dL), 100mg/dL, (≥300mg/dL, ≥1000mg/dL)
Glucose	Negative, 100mg/dL, 250mg/dL, 500mg/dL, ≥1000mg/dL	Negative, (100mg/dL, 250mg/dL), 500mg/dL, ≥1000mg/dL
Ketones	Negative, Trace, 15mg/dL, 40mg/dL, ≥80mg/dL, ≥160mg/dL	Negative, (Trace, 15mg/dL), 40mg/dL, (≥80mg/dL, ≥160mg/dL)
Hemoglobin (Occult blood)	Negative, Trace, Small, Moderate, Large	Negative, (Trace, Small), Moderate, Large
Leukocyte Esterase	Negative, Trace, Small, Moderate, Large	Negative, (Trace, Small), Moderate, Large

12.2.2 Vital sign assessments – abnormal

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

Table 12–5: Vital sign PCST criteria

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
Pulse Rate (beats/minute)	<6m	<100, >180
	6m - <3y	<90, >150
	3y - <12y	<60, >130
	12y - <17y	<50, >120
	≥17y	<50 and a decrease from Baseline of ≥15, >120 and an increase from Baseline of ≥15

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
Systolic Blood Pressure (mmHg)	<6m	<60, >100
	6m - <3y	<70, >120
	3y - <12y	<80, >140
	12y - <17y	<90, >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20, ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40, >65
	6m - <3y	<45, >75
	3y - <12y	<50, >80
	12y - <17y	<50, >105
	≥17y	<50 and a decrease from Baseline of ≥15, >105 and an increase from Baseline of ≥ 15
Respiratory Rate (breaths/minute)	<6m	<25, >55
	6m - <3y	<20, >45
	3y - <12y	<15, >35
	≥12y	<10, >25
Temperature	>1m	>101°F (38.3°C)
Body Weight	1m - <17y	<3% or 97% of the normal body weight growth curve ranges based on gender and the age of subject on date of weight assessment [a]
	≥17y	≥ 10% change from Baseline (an increase or a decrease) [a]

Abbreviations: m = month, y = year. A month is defined as 30 days; a year is defined as 365.25 days.
[a] source: http://www.cdc.gov/growthcharts/: Once the subject reaches 17 years of age use the body curve criteria of a 17-year-old regardless of their age in the study.

The following table is used to judge PCST regarding body weight.
Body weight (kg) at the 3 and 97 percentiles of the distribution at each age in Japanese children

Age (years-months)		16-0	16-1	16-2	16-3	16-4	16-5	16-6	16-7	16-8	16-9	16-10	16-11	17-0
Male	**3%**	45.66	45.89	46.11	46.33	46.53	46.73	46.93	47.11	47.29	47.47	47.64	47.80	47.97
	97%	83.83	84.08	84.32	84.57	84.82	85.07	85.31	85.56	85.79	86.02	86.24	86.45	86.64
Female	**3%**	41.04	41.11	41.18	41.25	41.31	41.37	41.43	41.49	41.55	41.60	41.66	41.71	41.76
	97%	69.91	69.98	70.05	70.12	70.19	70.25	70.31	70.36	70.41	70.46	70.51	70.55	70.59

Source: The Japanese Society for Pediatric Endocrinology: [homepage on the Internet]. Available from: http://jspe.umin.jp/pdf/fuhyo2.pdf

13 AMENDMENT TO THE STATISTICAL ANALYSIS PLAN (SAP)

13.1 Amendment 1

The main purpose for the SAP amendment 1 is to apply the modifications introduced up to Protocol Amendment 3 and 3.1. Moreover, many technical and detailed descriptions for executing the statistical analysis have been added in existing or new sections.

13.2 Amendment 2

Rationale for the amendment

The SAP is amended to reflect following changes adopted in Protocol Amendment 4 and Protocol Amendment 4.1.

- To reduce the total sample size from 504 to 444 study participants
- To reduce the minimum required number of Japanese study participants
- To add China Mainland to the list of participating countries and regions
- To update exclusion criteria 20 and 27
- To provide clarifications around the LEV use and LEV cap
- To update the study contact information
- To update the company name from SPRL to SRL

Modifications and changes

Global changes

There are no global changes to the SAP during this amendment.

Specific changes

Change #1

1 INTRODUCTION (last sentence)

… The SAP is based on the following study document: Protocol Amendment 3.0 and 3.1 (01 Feb 2019).

Has been changed to:

… The SAP is based on the following study document: Protocol Amendment 4 (10 Jan 2020).

Change #2

2.2.1.1 Primary efficacy variable

The primary efficacy variable is the partial seizure frequency per 28 days during the 12-week Treatment Period. The primary efficacy outcome is the percent reduction in partial seizure frequency over PBO based on analysis of covariance (ANCOVA).

Has been changed to:

2.2.1.1 Primary efficacy variable

The primary efficacy variable is the partial seizure frequency per 28 days during the 12-week Treatment Period. ~~The primary efficacy outcome is the percent reduction in partial seizure frequency over PBO based on analysis of covariance (ANCOVA).~~

Change #3

2.2.3 Primary Safety variable

The primary safety variable is adverse events (AEs).

Has been changed to:

2.2.3 Primary Safety variables

The primary safety variables are as follows:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of TEAEs leading to study withdrawal
- Incidence of treatment-emergent serious adverse events (SAEs)

Change #4

2.2.4 Exploratory Safety Variables

The exploratory safety variables are as follows:

- Laboratory tests (blood chemistry, hematology, urinalysis)
- Electrocardiogram (ECG)
- Vital signs
- Body weight
- …

Has been changed to:

2.2.4 Other Safety Variables

Other safety variables are as follows:

- Changes in clinical laboratory test parameters (blood chemistry, hematology, urinalysis)
- Electrocardiogram (ECG) parameters and findings

- Changes in vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate]
- Changes in body weight
- …

Change #5

2.3.1 Study duration per subject (second paragraph)

• Prior to entry into LTFU study or MAP, the informed consent should be obtained from the subject at the end of Treatment Period (Visit 7). …

Has been changed to:

• Prior to entry into LTFU study or MAP, the informed consent, where applicable, should be obtained from the subject at the end of Treatment Period (Visit 7). …

Change #6

2.3.2 Planned number of subjects and sites

The planned number of subjects who are evaluable for the primary efficacy analysis is 504 (168 subjects per treatment group). Of the 504 subjects, approximately 129 Japanese subjects and approximately 375 subjects from other countries will be randomized.

The number of prior LEV use subjects will be limited to 30% of the total study population. Considering an anticipated screen failure rate of approximately 20%, approximately 630 subjects (162 Japanese subjects and 468 subjects from other countries) will be screened. It is planned to have those subjects recruited in approximately 100 sites.

Has been changed to:

2.3.2 Planned number of subjects and sites

The planned number of evaluable subjects for the primary efficacy analysis is 444 (148 subjects per treatment group). The number of prior LEV use subjects will be limited to 30% of the total study population. Considering an anticipated screen failure rate of approximately 20%, approximately 555 subjects were to be screened. It is planned to have subjects recruited in approximately 95 sites.

Change #7

2.3.3 Anticipated regions and countries

The study is planned to be conducted in Japan, Taiwan, Philippines, Thailand, Singapore, and Malaysia, Hong Kong, Korea, Bulgaria, and Poland with possible extension to other countries or regions.

Has been changed to:

2.3.3 Anticipated regions and countries

The study is being conducted in Japan, Taiwan, China Mainland, Philippines, Thailand, Singapore, and Malaysia.

Change #8

2.4 Determination of sample size

A total of 168 analyzable subjects per treatment group will provide 80% power to simultaneously detect differences between BRV treatment groups (BRV 50mg/day group and BRV 200mg/day group) and PBO group at the 1-sided 0.025 significance level assuming treatment differences of 0.217 and 0.264 in means on the log-transformed scale and a common SD of 0.66. The estimates of 0.217 and 0.264 correspond to reductions of 19.5% and 23.2% of BRV over PBO after back-transformation, respectively. The percent reduction of 23.2% is obtained from BRV 200mg/day in the N01358 study. Based on a similar result from the Integrated Summary of Efficacy, a 19.5% reduction of BRV 50mg/day over PBO can be estimated. The SD of 0.66 is based on the observed SD from all treatment groups in N01358. The number of 168 subjects per treatment group will provide powers of 95% and 85% to detect the differences of BRV 200mg/day and BRV 50mg/day for PBO, respectively. Accordingly, a power to simultaneously detect differences of both BRV 200mg/day and BRV 50mg/day vs PBO will attain 81% (0.95×0.85). A total of 504 (168×3) analyzable subjects in the study is calculated as a target number.

Has been changed to:

A total of 148 analyzable subjects per treatment group will provide 80% power to simultaneously detect differences between BRV treatment groups (BRV 50mg/day group and BRV 200mg/day group) and the PBO group at the 1-sided 0.025 significance level. The sample size assumes treatment differences of 0.221 and 0.285 in means on the log-transformed scale and a common SD of 0.66. The estimates of 0.221 and 0.285 correspond to reductions of 19.8% and 24.8% of BRV over PBO after back-transformation, respectively. The percent reduction of 24.8% is obtained from BRV 200mg/day in the N01358 study and assuming the LEV cap of 30% is reached overall. Based on a similar result from the Integrated Summary of Efficacy and again assuming the LEV cap of 30% is reached overall, a 19.8% reduction of BRV 50mg/day over PBO can be estimated. The SD of 0.66 is based on the observed SD from all treatment groups in N01358. The sample size calculation accounts for the correlation of the test statistics (same placebo group is compared to each BRV dose) as well as the planned Hochberg procedure. A total of 444 (148×3) analyzable subjects in the study is calculated as a target number.

Change #9

3.1 General presentation of summaries and analyses (last paragraph)

All summary tables and figures will be presented overall and by racial subgroup, ie, for group “All”, “Japanese” and “Non-Japanese” unless stated otherwise.

Has been changed to:

All summary tables and figures will be presented overall and by Japan, unless stated otherwise. In addition, by-region subgroup analysis will be performed overall, by Japan, and by Non-Japan to the selected efficacy endpoints (see Section 4.7).

Change #10

3.2.1.2 End date of the Treatment Period

The end date of the Treatment Period will be either the date of Visit 7 for subjects completing the Treatment Period, or the date of the Early Discontinuation Visit (EDV) for subjects who discontinued during the Treatment Period. If a subject does not have a Visit 7/EDV, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of study drug during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

Has been changed to:

This section is removed.

Change #11

3.2.3 Last value

The Last value for laboratory tests, vital signs and ECG is a value collected in the last visit including unscheduled visits during a given period.

Has been changed to:

3.2.3 End of treatment value

The "End of treatment" value for laboratory tests, vital signs and ECG is a value collected in the last visit including unscheduled visits during the treatment period.

Change #12

3.4 Protocol deviations

Has been changed to:

3.4 Important Protocol deviations

Change #13

…Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL) version SEP 2017. Medical procedures will not be coded.

Has been changed to:

3.8 Coding dictionaries

Medical history and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL) version SEP 2017. Medical procedures will not be coded.

Change #14

3.8.6 Dose mapping for total daily BRV dose

Has been changed to:

3.9.6 Dose mapping for total daily BRV dose

(last paragraph is newly added)

In the circumstance the daily total blinded dose as recorded on the CRF exceeds the maximum nominal dose as described in the appendix Section 12.1, it is assumed the subject took the active treatment for all additional dosage. For example, suppose a BRV 200mg subject was recorded 275 mg/day total daily dose during the treatment period on the CRF (exceeding the maximum dose of 200 mg/day during the treatment period), it would be assumed the subject took active 200mg + 75 mg =275 mg/day.

Change #15

Section 3.11 is newly added:

3.11 Consideration for COVID-19

A new COVID-19 CRF, to evaluate the impact of global pandemic was created and implemented to collect the information on impacted visit, impact category, and relationship to COVID-19.

The impact on study conduct of the COVID-19 global pandemic will be assessed and captured as: confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 without infection or any other deviation from the protocol due to COVID-19.

Summary and listing (see Section 5.1.3) to describe the impact on the interpretability of efficacy and safety endpoint due to COVID-19 will be performed.

Summary and listing to describe the AE related to COVID-19 vaccination will be provided (see Section 10.2.1)

Change #16

4.3 Interim analyses and data monitoring

No formal interim analyses are planned for this study.

However, an informal analysis is planned post data collection during the double-blind period of the study to support regulatory submissions. Prior to the analysis, an official unblinding will be completed.

At a minimum, one interim report is planned. Regular monitoring of safety data collected during clinical studies will be performed by medically qualified Sponsor personnel or equivalent designee(s). Multicenter studies

Study outcomes will not be assessed for individual investigator sites due to the expected low enrollment within each investigator site and because the subject randomization is not stratified by investigator site. Treatment by investigator site interactions will not be assessed.

Has been changed to:

4.3 Interim analyses and data monitoring

No formal interim analyses are planned for this study.

Change #17

Multicenter studies

Study outcomes will not be assessed for individual investigator sites due to the expected low enrollment within each investigator site and because the subject randomization is not stratified by investigator site. Treatment by investigator site interactions will not be assessed.

Has been changed to:

4.4 Multicenter studies

Study outcomes will not be assessed for individual investigator sites due to the expected low enrollment within each investigator site and because the subject randomization is not stratified by investigator site. Treatment by investigator site interactions will not be assessed.

Change #18

4.6 Examination of subgroups

Selected efficacy outcomes will be evaluated for the following subgroup variables:

- Gender
- Categorized age (<17 years, 17 to <65 years, 65 years and older)
- Country (Japan, Taiwan, Philippines, Thailand, Singapore, Malaysia, Hong Kong, Korea, Bulgaria, and Poland)
- Region (Japan and Non-Japan)
- LEV use (LEV naive versus prior LEV use)
- Number of AEDs previously used but discontinued prior to study entry (≤2 versus >2)
- AED inducer status (use of an inducer at study entry versus no inducer at study entry)
- Seizure frequency by seizure type for seizure types IA, IB, and IC

All evaluations will be descriptive; neither statistical testing of treatment by subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out.

Has been changed to:

4.7 Examination of subgroups

Subgroup analysis will be conducted for the following efficacy outcomes:

• Percent reduction in partial seizure frequency (per 28 days during the 12-week Treatment Period) over PBO based on ANCOVA

• 50% responder rate based on percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

• Percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

The above selected efficacy outcomes will be evaluated for the following subgroup variables:

- Gender
- Categorized age (<17 years, 17 to <65 years, 65 years and older)
- Country (Japan, China Mainland, Philippines, Thailand, Taiwan, Singapore, and Malaysia, in which Taiwan and Singapore will be combined with Malaysia due to small number of enrolments)
- Region (Japan, non-Japan)
- LEV use (LEV naive, prior LEV use)
- Number of AEDs previously used but discontinued prior to study entry (≤2 versus >2)
- AED inducer status (use of an inducer at study entry versus no inducer at study entry)

The AED inducer will be captured according to the drug list provided by UCB.

- Seizure frequency by seizure type for seizure types IA, IB, and IC

All evaluations will be descriptive; neither statistical testing of treatment by subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out.

Change #19

New section 5.1.4 is added:

5.1.4 Stratification levels per CRF

During the conduct of the randomization, some subjects with the stratification levels of LEV status or number of previous AEDs mistakenly entered to the IVRS system. A sensitivity analysis using the actual stratification levels for LEV status and number of previous AEDs will be performed (see Section 8.1.2).

The actual LEV status will be captured from CRF form "History of Previous Antiepileptic Drug Treatment". Subjects will be considered with prior LEV use if levetiracetam is

captured in any preferred drug name in this CRF form. Otherwise, the subjects will be considered LEV naïve.

The number of AEDs previously used but discontinued prior to study entry will also be captured from CRF form "History of Previous Antiepileptic Drug Treatment" by counting the number of unique preferred drug name (≤2 vs >2 AEDs).

Change #20

6.1 Demographics

Age in years will be calculated based on date of Visit 1 and an incomplete birth date assuming birth of first day of the month (yyyy-mm-01) in the interactive voice/WEB response system.

Has been changed to:

6.1 Demographics

Age in years will be calculated based on date of informed consent and an incomplete birth date assuming birth on the first day of the month (yyyy-mm-01) in the interactive voice/WEB response system.

Change #21

6.4 History of previous AED use

Summaries in this section will be based on the History of Previous AED Treatment CRF which includes only AEDs stopped prior to study entry. In addition to the following summary tables, a corresponding subject data listing will be provided.

Has been changed to:

6.4 History of previous AED use

Previous AEDs are AEDs taken and discontinued prior to study entry. The history of previous AED will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol. However, investigator's judgement will be prioritized and taken into consideration. Summaries in this section will be based on the History of Previous AED Treatment CRF which includes only AEDs stopped prior to study entry.

For summaries by preferred drug name, some AEDs will be grouped as follows:

Valproate includes valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, ergenyl chrono, valproic acid.

Phenytoin includes phenytoin sodium, phenytoin calcium, mephenytoin, zentronal, metetoin, ethotoin, albutoin, hydantal, phelantin, hydantol D, anirrit, dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, hydantoin.

Phenobarbital includes phenobarbital sodium, methylphenobarbital, metharbital, alepsal, phenobarbital, kaneuron, epanal.

Benzodiazepine AEDs that can be grouped by bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate are considered the same AED at the group level.

Combination AEDs are not considered for grouping.

In addition to the following summary tables, a corresponding subject data listing will be provided.

Change #22

8.1.2 Primary analysis of the primary efficacy variable

Has been changed to:

8.1.2 Primary analysis of the primary efficacy variable

(last paragraph is newly added)

During the conduct of the randomization, some subjects with the stratification levels mistakenly entered to the IVRS system and a sensitivity analysis will be performed to assess the impact due to this error. The sensitivity analysis will be conducted to the primary efficacy variable using the similar ANCOVA model with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for treatment, an effect for country, and an effect for the 4 combinations of stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the actual stratification levels for LEV status and number of previous AEDs as entered in the CRF (see Section 5.1.4), and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate.

Change #23

8.2.1 Percent reduction in partial seizure frequency

Percent reduction from Baseline to the Treatment Period in partial seizure frequency will be calculated by subtracting 28 day adjusted Treatment Period partial seizure frequency [A] from 28 day adjusted Baseline Period partial seizure frequency [B], and multiplying the resulting quantity by 100 and dividing by the Baseline Period 28 day adjusted partial seizure frequency.

$$\%\text{Reduction} = 100 \times \frac{[\text{A}] - [\text{B}]}{[\text{B}]}$$

Has been changed to:

Percent reduction from Baseline to the Treatment Period in partial seizure frequency will be calculated by subtracting 28 day adjusted Treatment Period partial seizure frequency [A] from 28 day adjusted Baseline Period partial seizure frequency [B], and multiplying the resulting quantity by 100 and dividing by the Baseline Period 28 day adjusted partial seizure frequency.

$$\%\text{Reduction} = 100 \times \frac{[B] - [A]}{[B]}$$

Change #24

9.1 BRV plasma concentrations
Descriptive and inferential statistics in Section 3.1.1 for BRV observed plasma concentrations are computed per defined time window post-dose for all PK-PPS by actual dose given before each blood sampling for PK and dose normalized BRV plasma concentrations are computed for all doses with the same manner. 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.
…
• Time Window [-0 (Just before dosing), >0-1, >1-2, >2-4, >4-8, >8-10, >10-12, >12 hours post dosing]

Has been changed to:

9.1 BRV plasma concentrations
Descriptive and inferential statistics in Section 3.1.1 for BRV observed plasma concentrations are computed per defined time window post-dose (>0-4 hours, >4-8 hours, and >8 hours) for all PK-PPS by actual dose given before each blood sampling for PK and dose normalized BRV plasma concentrations are computed for all doses with the same manner. 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.
…
• Time Window [>0-4 hours, >4-8 hours, and >8 hours post dosing]

Change #25

10.1 Extent of exposure

(last paragraph)

… The number and percentage of subjects with the following categories of durations of study drug exposure for the Treatment Period and the entire study will also be summarized: ≤2 weeks, >2 weeks and ≤4 weeks, >4 weeks and ≤8 weeks, >8 weeks and ≤12 weeks, >12 weeks.

Has been changed to:

10.1 Extent of exposure

(last paragraph)

… The number and percentage of subjects with the following categories of durations of study medication exposure for the Treatment Period and the entire study will also be summarized:>0 weeks, >=2 weeks, >=4 weeks, >=6 weeks, >=8 weeks, >=10 weeks, and >=12 weeks.

Change #26

10.2.1 General summaries of AEs

A new summary table is added:

- Incidence of TEAEs related to COVID-19 vaccination

13.3 Amendment 3

Rationale for the amendment

The SAP is amended to change the stratification level used to the efficacy analyses from IVRS data to the actual stratification level according to the CRF data.

Modifications and changes

Change #1

Section 3.2.2 Study periods

Treatment Period	From the date of Visit 3 until the day of Visit 7 in subjects who complete the Treatment Period; or EDV in subjects who discontinue treatment early prior to Visit 7. If a subject does not have a Visit 7 or EDV date, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of IMP during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

Has been changed to:

Section 3.2.2 Study periods

Treatment Period	From the date of Visit 3 until the day of Visit 7 in subjects who complete the Treatment Period; or EDV in subjects who discontinue treatment early prior to Visit 7. A subject is considered starting Treatment Period if the subject enters Visit 3 and is randomized. If a subject does not have a Visit 7 or EDV date, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of IMP during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

Change #2

New section 3.2.4 is added:

3.2.4 Actual stratification level per CRF

During the conduct of the randomization, some subjects with the stratification levels of LEV status or number of previous AEDs mistakenly entered to the IVRS system. The actual stratification level will be derived according to the CRF data:

The LEV status per CRF (LEV naïve vs prior LEV use) will be captured from the CRF form "History of Previous Antiepileptic Drug Treatment". Subjects will be considered with prior LEV use if levetiracetam is captured in any preferred drug name in this CRF form. Otherwise, the subjects will be considered LEV naïve.

The number of AEDs previously used but discontinued prior to study entry per CRF (≤2 vs >2 AEDs) will also be captured from the CRF form "History of Previous Antiepileptic Drug Treatment" by counting the number of unique AED entered in this form. However, if the same compound name is also entered in the CRF form "Prior and Concomitant Medications", the drug is not counted as a previous AED because it is considered that the subject has taken the same AED concomitantly during the study. This was instructed in the CRF completion instruction regarding how to count the number of previous AED at the randomization.

The following AEDs will be considered the same AED at the group level while counting the number of previous AEDs:

- Valproate includes valproate sodium, valproate semisodium, valproate bismuth, valproate magnesium, valpromide, ergenyl chrono, valproic acid.
- Phenytoin includes phenytoin sodium, phenytoin calcium, mephenytoin, zentronal, metetoin, ethotoin, albutoin, hydantal, phelantin, hydantol D, anirrit, dintoinale, fosphenytoin sodium, phenytoin, fosphenytoin, hydantoin derivatives, hydantoin.
- Phenobarbital includes phenobarbital sodium, methylphenobarbital, metharbital, alepsal, phenobarbital, kaneuron, epanal.
- Benzodiazepine AEDs are grouped separately by bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate.

Change 3

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of study drug and have at least 1 post-Baseline seizure daily record card (DRC) data. Both primary and secondary efficacy analyses will primarily be carried out using the FAS.

Has been changed to:

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of study drug and have at least 1 post-Baseline seizure daily record card (DRC) data during the Treatment Period. Both primary and secondary efficacy analyses will primarily be carried out using the FAS.

Change 4

4.1 Adjustments for covariates

...

In this regard, the primary analyses based on ANCOVA will include an effect for treatment, an effect for country, and an effect for the 4 combinations of levels for LEV status and number of previous AEDs. Lower-enrolling countries will be pooled as described below.

Has been changed to:

4.1 Adjustments for covariates

…

In this regard, the primary analyses based on ANCOVA will include an effect for treatment, an effect for country, and an effect for the 4 combinations of levels for LEV status and number of previous AEDs. The actual stratification level (see Section 3.2.4) will be used for the primary analyses. Lower-enrolling countries will be pooled as described below.

Change 5

4.7 Examination of subgroups

…

- LEV use (LEV naive, prior LEV use)
- Number of AEDs previously used but discontinued prior to study entry (≤2 versus >2)
- AED inducer status (use of an inducer at study entry versus no inducer at study entry)

  The AED inducer will be captured according to the drug list provided by UCB.
- Seizure frequency by seizure type for seizure

Has been changed to:

4.7 Examination of subgroups

…

- LEV use (LEV naive, prior LEV use) according to actual stratification level as per the CRF
- Number of AEDs previously used but discontinued prior to study entry (≤2 versus >2) according to actual stratification level as per the CRF
- AED inducer status (use of an inducer at study entry versus no inducer at study entry)

  The AED inducer will be captured according to the drug list provided by UCB.
- ~~Seizure frequency by~~ Seizure type ~~for seizure~~ at Baseline (types IA, IB, and IC)

  Subjects who experience at least one type of IA, IB, and IC seizure, respectively, during the Baseline Period will be included in the analysis for that seizure type. Subjects may be classified into more than 1 subgroup based on their baseline seizure profile.

Change #6

5.1.1 Overall subject disposition

…

Down-Titration Period Disposition

- The number of subjects entering the Down-Titration Period
- The number of subjects completing the Down-Titration Period

  The number of subjects completing the Study Drug -Free Period (ie, subjects with Safety Visit).

Has been changed to:

5.1.1 Overall subject disposition

…

Down-Titration Period Disposition

- The number of subjects entering the Down-Titration Period
- The number of subjects completing the Down-Titration Period

  A subject is considered completing the Down-Titration Period if this subject also completes the Study Drug -Free Period ~~(ie, subjects with Safety Visit)~~.

Change #7

5.1.1 Overall subject disposition

…

Open-Label Temporary Period and MAP are not applicable to subjects enrolled in Japan and China.

In addition to the overall summary of disposition, the above will also be summarized by LEV status, and number of previous AEDs (≤2 versus >2).

Has been changed to:

5.1.1 Overall subject disposition

…

Open-Label Temporary Period and MAP are not applicable to subjects enrolled in Japan and China. Percentages for Open-Label Temporary Period will be relative to the number of subjects entering the Open-Label Period in the RS.

In addition to the overall summary of disposition, the above will also be summarized by LEV status, and number of previous AEDs (≤2 versus >2) according to the actual stratification level as per the CRF.

Change #8

5.1.4 Stratification levels per CRF

During the conduct of the randomization, some subjects with the stratification levels of LEV status or number of previous AEDs mistakenly entered to the IVRS system. A sensitivity analysis using the actual stratification levels for LEV status and number of previous AEDs will be performed (see Section 8.1.2).

The actual LEV status will be captured from CRF form "History of Previous Antiepileptic Drug Treatment". Subjects will be considered with prior LEV use if levetiracetam is captured in any preferred drug name in this CRF form. Otherwise, the subjects will be considered LEV naïve.

The number of AEDs previously used but discontinued prior to study entry will also be captured from CRF form "History of Previous Antiepileptic Drug Treatment" by counting the number of unique preferred drug name (≤2 vs >2 AEDs).

Has been changed to:

5.1.4 Number of subjects by stratification levels

The number and percentage of randomized subjects for each level of LEV status (never used LEV versus prior LEV use only), and number of AEDs previously used but discontinued prior to study entry (≤2 versus >2) will be summarized overall per the data entered in IVRS system and per the actual levels according to the CRF data, separately.

The number and percentage of randomized subjects with discrepancies between the IVRS stratification and the actual stratification levels identified on the CRF will be summarized for LEV status and number of previous AEDs.

Additionally, the number and percentage of randomized subjects by country will be summarized.

Change #9

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized by treatment group, over all subjects on BRV treatment and over all subjects. Unless otherwise specified, tables will be provided for the SS and listings will be done for the ES.

Has been changed to:

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized by treatment group, over all subjects on BRV treatment and over all subjects. Unless otherwise specified, tables will be provided for the ~~SS~~ FAS and listings will be done for the ES.

Change #10

6.2.3 History of epileptic seizures

…

The epilepsy duration (years) will be derived as the date of informed consent minus the date of the first diagnosis (yyyy-mm-01), which is similar to the derivation of age. For subjects who only have a year of the diagnosis date, the date of January 1 will be assumed. If an imputed date of the diagnosis is less than the date of birth due to the application of imputation rules, then set epilepsy duration equal to the subject's age.

Has been changed to:

6.2.3 History of epileptic seizures

…

The epilepsy duration (years) will be derived as the date of informed consent minus the date of the first diagnosis (yyyy-mm-01), which is similar to the derivation of age. For subjects who only have a year of the diagnosis date, the date of January 1 will be assumed. If an imputed date of the diagnosis is less than the date of birth due to the application of imputation rules, then set epilepsy duration equal to the subject's age. No imputation will be done for completely missing diagnosis date and epilepsy duration will not be calculated for subjects with completely missing diagnosis date.

Change #11

6.2.3 History of epileptic seizures

…

For partial dates of birth and first diagnosis of epilepsy, imputation rules are applied. If an imputed date of first diagnosis of epilepsy is less than the date of birth due to the application of imputation rules, then set the date of first diagnosis of epilepsy to the date of birth.

Has been changed to:

6.2.3 History of epileptic seizures

…

For partial dates of birth and first diagnosis of epilepsy, imputation rules are applied. If an imputed date of first diagnosis of epilepsy is less than the date of birth due to the application of imputation rules, then set the date of first diagnosis of epilepsy to the date of birth. For completely missing dates of first diagnosis of epilepsy, no imputation will be done and age at time of first seizure will not be calculated.

Change #12

6.3.1 Previous and ongoing medical history

The number and percentage of subjects with a medical history condition, including both resolved and ongoing conditions at the time of study entry, will be summarized overall and by MedDRA primary system organ class (SOC) and preferred term (PT).

Has been changed to:

6.3.1 Previous and ongoing medical history

The number and percentage of subjects with a medical history condition, including both resolved and ongoing conditions at the time of study entry, will be summarized overall and by MedDRA primary system organ class (SOC) and preferred term (PT) according to the SS.

Change #13

6.4 History of previous AED use

Previous AEDs are AEDs taken and discontinued prior to study entry. The history of previous AED will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol. However, investigator's judgement will be prioritized and taken into consideration. Summaries in this section will be based on the History of Previous AED Treatment CRF which includes only AEDs stopped prior to study entry.

For summaries by preferred drug name, some AEDs will be grouped as follows:

…

Has been changed to:

6.4 History of previous AED use

Previous AEDs are AEDs taken and discontinued prior to study entry. The history of previous AED will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol. However, investigator's judgement will be prioritized and taken into consideration. Summaries in this section will be based on the History of Previous AED Treatment CRF which includes only AEDs stopped prior to study entry.

For summaries by preferred drug name, some AEDs will be grouped as follows (same grouping rules in Section 3.2.4:):

…

Change #14

6.4.1 Number of previous AEDs

The number of previous AEDs will be summarized based on the following categorization: 0-1, 2-4, and ≥5 AEDs.

Has been changed to:

6.4.1 Number of previous AEDs

The number of previous AEDs will be summarized based on the following categorization: 0-1, 2-4, and ≥5 AEDs. When counting the number of previous AED from the CRF form "History of Previous Antiepileptic Drug Treatment", if the same compound name is also entered in the CRF form "Prior and Concomitant Medications", the drug is not counted as a previous AED (see Section 3.2.4).

Change #15

6.5 Concomitant medications

…

Concomitant AEDs (including AEDs taken at study entry) will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol.

Has been changed to:

6.5 Concomitant medications

…

Concomitant AEDs (including AEDs taken at study entry) will be recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol and will be captured according to the CRF "Core AED?" based on the investigator's judgement.

Change #16

6.5.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AED medications at the time of study entry will be summarized by WHO DRL pharmacological group and preferred drug name.

Has been changed to:

6.5.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AED medications at the time of study entry will be summarized by WHO DRL pharmacological group and preferred drug name according to the SS.

Change #17

8.1.2 Primary analysis of the primary efficacy variable

The primary efficacy outcome will be the percent reduction in partial seizure frequency per 28 days during the Treatment Period of each BRV treatment individually over PBO.

The primary analysis will be based on ANCOVA with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for treatment, an effect for country, and an effect for the 4 combinations of stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the IVRS data, and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate. Lower enrolling countries will be pooled for this analysis as described in Section 4.1.

…

During the conduct of the randomization, some subjects with the stratification levels mistakenly entered to the IVRS system and a sensitivity analysis will be performed to assess the impact due to this error. The sensitivity analysis will be conducted to the primary efficacy variable using the similar ANCOVA model with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for

treatment, an effect for country, and an effect for the 4 combinations of stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the actual stratification levels for LEV status and number of previous AEDs as entered in the CRF (see Section 5.1.4), and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate.

Has been changed to:

8.1.2 Primary analysis of the primary efficacy variable

The primary efficacy outcome will be the percent reduction in partial seizure frequency per 28 days during the Treatment Period of each BRV treatment individually over PBO.

The primary analysis will be based on ANCOVA with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for treatment, an effect for country, and an effect for the 4 combinations of actual stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the ~~IVRS~~ CRF data (see Section 3.2.4), and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate. Lower enrolling countries will be pooled for this analysis as described in Section 4.1.

…

During the conduct of the randomization, some subjects with the stratification levels mistakenly entered to the IVRS system and a sensitivity analysis will be performed to assess the impact due to this error. The sensitivity analysis will be conducted to the primary efficacy variable using the similar ANCOVA model with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency as the outcome and an effect for treatment, an effect for country, and an effect for the 4 combinations of stratification levels for LEV status and number of previous AEDs (≤2 versus >2) according to the ~~actual stratification levels for LEV status and number of previous AEDs as entered in the CRF~~ IVRS data, and log-transformed 28-day adjusted Baseline partial seizure frequency as a continuous covariate.

Change #18

8.2.6 Time to nth partial seizure

…

Time to nth partial seizure will be compared between each BRV treatment group and PBO using a semi-parametric proportional hazards regression model with an effect for country, an effect for the 4 combinations of levels for LEV status and number of previous AEDs (≤2 versus >2) and log transformed Baseline partial seizure frequency as a continuous covariate. Significance probabilities (ie, p values) and hazard ratios and corresponding two-sided 95% CIs will be presented for the comparison of each BRV treatment group to PBO. Lower enrolling countries will be pooled for this analysis as described in Section 4.1.

Has been changed to:

8.2.6 Time to nth partial seizure

…

Time to nth partial seizure will be compared between each BRV treatment group and PBO using a semi-parametric proportional hazards regression model with an effect for country, an effect for the 4 combinations of actual stratification levels for LEV status and number of previous AEDs (≤2 versus >2) per the CRF data, and log transformed Baseline partial seizure frequency as a continuous covariate. Significance probabilities (ie, p values) and hazard ratios and corresponding two-sided 95% CIs will be presented for the comparison of each BRV treatment group to PBO. Lower enrolling countries will be pooled for this analysis as described in Section 4.1.

Change #19

10.2.1 General summaries of AEs

…

New summary tables are added:

- Incidence of drug-related TEAEs by study period (Treatment, Down-Titration, Study Drug-Free, and Transition Periods)
- Incidence of TEAEs leading to discontinuation of study

Change #20

10.2.1 General summaries of AEs

…

For the summary by maximum intensity, each subject will be counted at most once per primary SOC or PT according to the maximum intensity of all AEs within that SOC or PT. Severe intensity will be assumed for AEs for which intensity is not specified.

Has been changed to:

10.2.1 General summaries of AEs

…

For the summary by maximum intensity and by maximum relationship, each subject will be counted at most once per primary SOC or PT according to the maximum intensity and the maximum relationship of all AEs within that SOC or PT. For the summary by intensity and by relationship, a subject may be counted more than once according to the intensity of the TEAEs and the relationship assessments.

Change #21

10.3.1 Hematology, Biochemistry and Urinalysis parameters

Hematology, biochemistry, and urinalysis parameters are assessed at Visits 1, 3 through 7, EDV, Visit 8, and the Safety Visit and may also be assessed at unscheduled visits.

Observed results as well as change from baseline will be analyzed descriptively for all laboratory parameters by visit and End of Treatment. Incidence of possibly clinically significant treatment-emergent (PCST) results will be summarized in the form of shift tables (from Baseline to End of Treatment) for hematology, blood chemistry and urinalysis parameters, if applicable. The PCST criteria are defined in Section 12.2.1.

…

Has been changed to:

10.3.1 Hematology, Biochemistry and Urinalysis parameters

Hematology, biochemistry, and urinalysis parameters are assessed at Visits 1, 3 through 7, EDV, Visit 8, and the Safety Visit and may also be assessed at unscheduled visits.

Observed results as well as change from baseline will be analyzed descriptively for all laboratory parameters by visit and End of Treatment. Incidence of possibly clinically significant treatment-emergent (PCST) results, PCST low value, and PCST high value will be summarized ~~in the form of shift tables (from Baseline to End of Treatment)~~ for hematology, blood chemistry and urinalysis parameters, if applicable. The PCST criteria are defined in Section 12.2.1.

…

Change #22

10.4.1 Vital signs

…

The number and percentage of subjects with at least one PCST low values, and subjects with at least one PCST high value will be summarized for SBP, DBP, pulse rate, and body weight for the Treatment Period and overall for the combined Treatment, Transition, Down-Titration, and Study Drug-Free Periods.. Percentages will be relative to the number of subjects with an assessment within each study period. PCST criteria are defined in Section 12.2.2.

Has been changed to:

10.4.1 Vital signs

…

The number and percentage of subjects with at least one PCST low values, and subjects with at least one PCST high value will be summarized for SBP, DBP, pulse rate, and body weight ~~for the Treatment Period and overall for the combined Treatment, Transition, Down-Titration, and Study Drug-Free Periods.~~. Percentages will be relative to the number of subjects with an assessment within each study period. PCST criteria are defined in Section 12.2.2.

Change #23

10.4.6 Neurological examination

A neurological examination is performed at Visits 1, 3, and 7/EDV, Visit 8 and at the Safety Visit and may also be performed at unscheduled visits. A listing of abnormal neurological examination findings will be provided ; no summaries of neurological examination findings are planned.

Has been changed to:

10.4.6 Neurological examination

A neurological examination is performed at Visits 1, 3, and 7/EDV, Visit 8 and at the Safety Visit and may also be performed at unscheduled visits. A listing of ~~abnormal~~ neurological examination ~~findings~~ results will be provided ; no summaries of neurological examination findings are planned.

Change #24

10.4.7 Psychiatric and mental status

An evaluation of Psychiatric and Mental Status is performed at Visits 1, 3, and 7/EDV, Visit 8 and at the Safety Visit and may also be performed at unscheduled visits. A listing of abnormal Psychiatric and Mental Status findings will be provided; no summaries of Psychiatric and Mental Status findings are planned.

Has been changed to:

10.4.7 Psychiatric and mental status

An evaluation of Psychiatric and Mental Status is performed at Visits 1, 3, and 7/EDV, Visit 8 and at the Safety Visit and may also be performed at unscheduled visits. A listing of ~~abnormal~~ Psychiatric and Mental Status ~~findings~~ results will be provided; no summaries of Psychiatric and Mental Status findings are planned.

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

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