

STATISTICAL ANALYSIS PLAN

Study: EP0087

Product: Brivaracetam

A Multicenter, Open-label, Randomized, Parallel-Group, Active-Controlled Study to Assess the Efficacy and Safety of Brivaracetam Administered Intravenously as Treatment for Increased Seizure Activity in an Epilepsy Monitoring Unit Setting

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LIST OF ABBREVIATIONS

AC	active control
AE	adverse event
AED	antiepileptic drug
BMI	body mass index
BRV	Brivaracetam
CF	conversion factor
CRF	case report form
D	Day
DBP	diastolic blood pressure
DEM	data evaluation meeting
ECG	electrocardiogram
EEG	electroencephalogram
EMU	epilepsy monitoring unit
eg	exempli gratia=for example
ER	emergency room
H	hour/-s
HDL	high-density lipoproteins
ILAE	International League Against Epilepsy
IPD	Important Protocol Deviations
ITT	Intent-to-Treat
ITT-R	Intent-to-Treat as randomized
ITT-T	Intent-to-Treat as treated
iv	Intravenous
IVRS	interactive voice response system

KM	Kaplan-Meier
LDL	low-density lipoprotein
LEV	levetiracetam
LOQ	limit of quantification
LZP	Lorazepam
MIN	Minutes
MedDRA	Medical Dictionary for Regulatory Activities
PCST	possibly clinically significant treatment-emergent
PK	Pharmacokinetic
POS	partial onset seizure
PP	per protocol
PPS	Per-Protocol Set
PR	pulse rate
PRO	patient reported outcome
PT	preferred term
RR	respiratory rate
RS	Randomized Set
SAE	serious adverse event
SAGE	self-administered gerocognitive examination
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety follow-up
SOC	system organ class

TEAE

treatment-emergent adverse event

WHO-DRL

World Health Organization Drug Reference List

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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 1: 26 May 2016.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to assess the efficacy of iv brivaracetam (BRV) compared to iv lorazepam (LZP) in subjects with epilepsy undergoing epilepsy monitoring unit (EMU) evaluation who experience seizures that require prompt treatment.

2.1.2 Secondary objective

The secondary objective is to compare the safety and tolerability of iv BRV and iv LZP in subjects with epilepsy undergoing EMU evaluation who experience seizures that require prompt treatment.

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable is the time to next seizure (per clinical observation with EEG confirmation) or rescue medication.

2.2.1.2 Secondary efficacy variables

- Time to next seizure (per clinical observation) or rescue medication
- Proportion of subjects seizure-free per clinical observation at 6 hours, 8 hours, and 12 hours after the end of study drug administration
- Proportion of subjects who receive rescue medication during the 6 hours, 8 hours, and 12 hours after the end of study drug administration

2.2.1.3 Other efficacy variables

Time until seizure is resolved without additional intervention per clinical observation (only for those actively seizing at the end of study drug administration)

2.2.2 Pharmacokinetic variable

Plasma concentration of BRV at 1 hour and 5 hours after the end of BRV study drug administration.

2.2.3 Safety variables

- Adverse events
- Assessment of cognitive impairment

- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate [PR], and respiratory rate [RR])
- Oxygen saturation (measured by pulse oximetry)
- ECG
- Occurrence of status epilepticus

2.3 Study design and conduct

This study is an open-label, randomized, parallel-group, active-controlled study to assess the efficacy and safety of brivaracetam (BRV) administered intravenously as treatment for increased seizure activity in an epilepsy monitoring unit (EMU) setting.

Subjects will be 18 to 70 years of age, will have an established diagnosis of epilepsy, and will be admitted to an institution's EMU for seizure characterization or noninvasive presurgical evaluation. Upon admission to the EMU and after screening, the subject will be randomly assigned (1:1:1) to receive a single iv dose of BRV 100mg, BRV 200mg, or LEP. The number of subjects using levetiracetam (LEV) as concomitant AED will be limited to 25% of the total number of subjects who receive study drug.

Study drug administration will begin when the Investigator or designee determines by clinical observation and EEG that a seizure requiring intervention (ie, qualifying seizure) has started. Study drug administration will begin within 30 minutes of the qualifying seizure. A qualifying seizure event is defined as any one of the following circumstances, requiring intervention in the opinion of the Investigator:

- ≥ 3 seizures per 24 hours
- ≥ 2 seizures in 6 hours
- Any generalized tonic-clonic seizure requiring intervention, as determined by the Investigator

The subject's seizure activity by clinical observation will be assessed over the next 12 hours following the end of study drug administration. The dose and regimen of concomitant AEDs should remain stable after study drug administration during the Treatment Period unless the subject needs rescue medication. In addition, the subject's cognitive impairment, vital signs, oxygen saturation, and ECG will be measured at specified time points. Blood samples will be obtained at specified time points.

If the subject is seizure-free for the 12 hours following the end of study drug administration, the Treatment Period is concluded and other AEDs may be administered at the Investigator's discretion. The subject is then in the Safety Follow-up (SFU) Period, which lasts until 24 hours after the end of study drug administration.

If the subject's seizure activity does not stop after administration of study drug or seizure activity recurs, the subject may receive rescue medication (not from study drug supplies) at the Investigator's discretion. At the time of rescue medication administration, the Treatment Period is concluded, the subject is in the SFU Period, and subject may be subsequently treated with AEDs at the discretion of the Investigator.

The total duration of the study will be up to 4.5 weeks, inclusive of the Screening Period.

Screening Period (Visit 1 – Screening and Visit 1 – Prior to randomization): lasts up to 28 days for consenting, planning EMU stay, randomization, and inpatient EMU time prior to the seizure qualifying for study drug administration.

Treatment Period (Visit 2): beginning at start of study drug administration up to 12 hours following the end of study drug administration.

Safety Follow-Up Period (Visit 3): 24 hours following the end of study drug administration.

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

Approximately 60 subjects will be enrolled in order to have approximately 45 total subjects (15 subjects per group) qualifying for primary analysis at up to 20 sites.

2.4 Determination of sample size

The study is intended to demonstrate proof of concept. The sample size is not based on statistical calculation. Approximately 45 subjects (approximately 15 subjects per treatment group) will receive the study medication and qualify for the primary analysis.

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, standard deviation (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 0.001 will be presented as “<0.001” and p-values greater than 0.9999 will be presented as “>0.9999”. The rounded value of p-values ≥ 0.001 and ≤ 0.999 will be displayed. P-values exactly equal to 1 should be shown as 1.00.

Summaries for disposition, protocol deviations, demographics and baseline characteristics, medical history, AEDs and non-AEDs will present results for individual treatment groups and all BRV 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 all BRV groups combined.

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. In such cases, unless otherwise specified, the analysis will be run both with and without the values. 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.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day and time

For measurements with date and time collected, relative day and time will be calculated. The date and time format in this study is dd-MMM-yyyy HH:mm.

Relative day and time in 24-h clock will be calculated as current date minus first dose date, current time in hours minus first dose time in hours, current time in minutes minus first dose time in minutes (add 1 minute if the current date and time is the same or after the first dose date and time). Then adjust to the number of hours (h) in between two dates and times. Consider one day has 24 hours, 1 minute (min) = 1/60 h. Round the result to the second decimal. If the relative day is zero, then don't display zero days, display non-zero hours. When the relative day and relative hour equal to "0", there is no relative minute "0", if the current date and time is the same as the first dose date and time, the relative minute is "1". If the current date and time is prior to the first dose date and time, then the relative day and time will be denoted by "-". The relative day and time in the tables and listings will be displayed in hours.

Example 1: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 5-Jan-2017: 8:45 am. The relative day and time is calculated as 5-Jan-2017 minus 5-Jan-2017=0, 8:00 h – 10:00 h = -2:00 h, 45 min-30 min=15 min. The relative day and time is 0 d 1 h 45 min, i.e. -1 h 45 min or -1.75 h.

Example 2: first dose date and time is 5-Jan-2017: 10:30: am. The current date and time is 7-Jan-2017: 8:45 am. The relative day and time is calculated as 7-Jan-2017 minus 5-Jan-2017=2 d (48 h), 8:00 h – 10:00 h = -2:00 h, 45 min-30 min + 1 min=16 min. The relative day and time is 1 d 22 h 16 min or 46.27 h.

Example 3: first dose date and time is 5-Jan-2017: 10:30 am. The current date and time is 3-Jan-2017: 8:45 am. The relative day and time is calculated as 3-Jan-2017 minus 5-Jan-2017=-2 d (-48 h), 8:00 h – 10:00 h = -2:00 h, 45 min-30 min=15 min. The relative day and time is -2 d 1 h 45 min or 49.75 h.

Relative day and time will not be calculated for partial dates and times.

3.2.1.2 Relative day

For measurements with only date collected, relative day be calculated. The date format in the study is dd-MMM-yyyy.

Relative day will be calculated as the current date minus the date of first dose of study drug for days prior to the 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 day of first dose of study drug and prior to or on the day of last study drug dose (e.g., 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, relative day will be calculated as the current date minus the date of last dose of study drug and including a "+" to denote post-treatment days (e.g., the day after the last dose will be Day +1). Relative day will not be calculated for partial dates.

3.2.2 Study periods for analysis

The following study periods will be defined:

3.2.2.1 Screening Period

The Screening Period can start as early as on Day -28 until Day -1; it includes consenting, planning for EMU stay, randomization, inpatient EMU time prior to the seizure qualifying for study drug administration. The Screening Period Visit 1 consists of two parts Visit 1 - Screening and Visit 1 - Prior to randomization. Measurements with the date and time prior to the start date and time of study drug administration are in the Screening Period.

3.2.2.2 Treatment Period

The Treatment Period begins when the subject has a qualifying seizure (see [Section 2.3](#)) and study drug is administered and lasts up to 12 hours after the end of study drug administration or until a seizure occurs or a rescue medication is given. The start date and time of the Treatment Period is the start date and time of study drug administration. The end date and time of the Treatment Period is defined as the minimum of:

- end date and time of the first dose at Visit 2 plus 12 hours
- start date and time of the next seizure (see [Section 8.1.1](#) for next seizure definition)
- start date and time of the first rescue medication (see [Section 8.1.1](#) for first rescue medication definition)

Note, if a seizure occurs during the study drug administration (after start of the infusion and prior to the end of infusion) the seizure will not be counted when assessing time to first seizure efficacy endpoints. If rescue medication started prior to the end date and time of the study drug administration, then the treatment period end date and time is end date and time of the first dose plus 1 minute.

3.2.2.3 Safety Follow-Up Period

The Safety Follow-Up Period begins from the end of the treatment period and ends 24 hours after the end of study drug administration.

3.3 Definition of Baseline values

Baseline for laboratory variables (blood chemistry and hematology), vital signs, and oxygen saturation variables is defined as the value measured at screening. This is because it may be impossible to obtain saturation and vital signs for the subjects actively seizing at the start of study drug administration.

Baseline for body weight, cognitive impairment (Self-Administered Gerocognitive Examination (SAGE)) variables is defined as the last value prior to the start date and time of study drug administration. Both scheduled and unscheduled assessments are considered. Assessments taken on the date of study drug administration without a reported time will not be considered for baseline assessments (eg, will be assumed to have been taken after the start time of study drug administration).

Baseline should be determined separately for each individual laboratory variable and each individual vital sign variable. An exception is blood pressure, where a complete set of both systolic and diastolic blood pressure should be selected for baseline.

3.4 Protocol deviations

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

3.5 Analysis sets

3.5.1 All Subjects Screened Set

All Subjects Screened Set consists of all subjects who signed informed consent.

3.5.2 Randomized Set

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

Algorithmically, the RS will consist of all subjects who have a randomization number recorded on the CRF. This rule applies without exception. In particular, there will be no effort to address mis-randomizations in the statistical algorithms when defining the RS. The decision how to handle mis-randomizations with regard to CRF completion is a separate issue from the statistical algorithms.

The RS is generally used for summaries of subject disposition.

3.5.3 Intent-to-Treat Set

The Intent-to-Treat (ITT) Set will consist of all randomized subjects who received the study drug for qualifying seizures. All efficacy analyses will be carried out using the ITT Set as randomized (ITT-R) and safety analyses will be carried out using the ITT Set as treated (ITT-T).

3.5.4 Per-Protocol Set

The Per-Protocol (PP) Set will consist of all subjects in the ITT-R Set who did not have any important protocol deviations determined to impact the interpretation of the primary efficacy analysis. The primary efficacy analysis and select supportive efficacy analyses will be carried out using the PP Set.

3.5.5 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects in the ITT-R Set who provide at least one measurable post-Baseline plasma sample (with recorded sampling time). This analysis set will be used for the PK summary and listing.

3.6 Treatment assignment and treatment groups

Incorrectly treated subjects will be evaluated during the data evaluation meeting to assess the potential impact of such cases and any special considerations for statistical analyses. In general, subjects who receive the incorrect study medication will be analyzed according to the randomized treatment group for efficacy analyses and according to the treatment received for safety analysis. Any special cases (eg, subject receives both treatments) will be assessed at a data evaluation meeting and analysis decisions will be recorded in meeting minutes. This case is unexpected given there is only one study medication administration in this study.

Results for the active control (AC) are displayed in the left-most treatment column for tables for which the treatment arms are displayed across the top of the table and displayed as the first treatment in the first column for tables with treatment arms displayed down the page.

BRV treatment arms (BRV 100 mg, BRV 200 mg) are displayed in order by ascending dose either to the right of or below the AC arm (LZP), depending on the format of the table.

3.7 Center pooling strategy

No center pooling is planned for this study.

3.8 Coding dictionaries

Medical history and Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or later. Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL) version March 2016 or later. Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

The ECG measurements are collected as categorical measurements only; no quantitative ECG measurements will be collected. Therefore, ECG will not be summarized as observed values and changes from baseline using continuous descriptive statistics.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable to this study.

4.2 Handling of dropouts or missing data

There will be no specific imputation of missing data except for missing dates and/or times for concomitant medication and AE.

The handling of missing dates and times for seizures if applicable will be discussed during the Data Evaluation Meeting (DEM).

4.2.1 Handling of prior and concomitant medications with missing data

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

Imputation of Partial Start Dates:

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

Imputation of Partial End Dates:

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

There will be no imputation of any other missing data.

4.2.2 Handling of adverse events with missing data

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

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

- Imputations for missing end dates/times will not be performed for classification as treatment-emergent as this is not required.

Adverse events with missing severity or causality will be regarded as 'severe' and 'related' respectively for the tabulations. There will be no imputation of any other missing data. Any AE with additional missing data that prohibits classification for a given tabulation will be excluded from that tabulation.

In case of uncoded AEs, these AEs should be designated as "UNCODED" at all MedDRA levels, and such AEs will be included in summary tables and subject listings based on this classification.

4.3 Interim analyses and data monitoring

No formal interim analyses are planned for this study. A periodic safety signal evaluation will be carried out using safety data as part of the ongoing monitoring of safety for BRV.

4.4 Multicenter studies

Study outcomes will not be assessed for individual investigator sites because the subject randomization is not stratified by investigator site.

4.5 Multiple comparisons/multiplicity

Not applicable to this study. The study is not statistically powered and all p-values resulting from the statistical tests are exploratory only. No claims can be made based on these p-values.

4.6 Use of an efficacy subset of subjects

The subset of ITT-R subjects actively seizing at the end of study drug administration will be used for the analysis of time to seizure resolution without intervention.

The Per-Protocol Set will be used for the efficacy analysis. This analysis set will provide additional information on the efficacy analysis and will describe findings in a subset of subjects who more closely followed the intentions of the study protocol.

Other than the planned analyses based on PPS and the subset of subjects actively seizing at the end of study drug administration, no other efficacy subsets are defined for statistical analyses.

4.7 Active-control studies intended to show equivalence

Not applicable to this study.

4.8 Examination of subgroups

The subgroup that may be examined is:

- LEV Use (Yes/No)

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of screen failures and the primary reason for screen failure (eg. for no qualifying seizure) will be summarized for all screened subjects (ie, all subjects signing informed consent).

The date of first subject in (earliest Visit 1 date), date of last subject out (latest scheduled or unscheduled visit), and the number of screened subjects will be summarized for all study sites and by study site. Additionally, the number of subjects in each of the RS, ITT-R, ITT-T and PPS will be summarized for all treatment groups combined and by individual treatment group for all study sites and by study site.

The overall summary of disposition for randomized subjects will present the number and percentage of subjects for the following:

General Disposition of Analysis Sets

Subjects randomized to study drug (Randomized Set)

Subjects receiving study drug as randomized (Intent-to-Treat as Randomized Set)

Subjects receiving study drug as treated (Intent-to-Treat as Treated Set)

Per-Protocol Set

General Disposition End of Study

Subjects completing the study

Subjects discontinuing the study and the primary reason for discontinuation

Discontinuation due to Adverse Events

All percentages will be relative to the number of randomized subjects.

Subject disposition, subject analysis sets, study eligibility criteria, subjects who did not meet study eligibility criteria listings will be provided on all subjects screened. Study discontinuation listing will be provided on randomized set.

5.2 Protocol deviations

The number and percentage of randomized subjects with no important protocol deviations and at least 1 important protocol deviation will be summarized overall, and by main category of protocol deviation. Additionally, the number and percentage of subjects excluded from the PPS due to important protocol deviations will be summarized overall and by main protocol deviation category for the ITT-R. Main categories of protocol deviations are inclusion criteria, exclusion criteria, withdrawal criteria, prohibited concomitant medication use, incorrect treatment or dose, treatment non-compliance and procedural non-compliance. Other specific categories of protocol deviations will be defined within the IPD specifications. Important protocol deviations listing will be provided on randomized set. Subjects excluded from Per-Protocol Analysis Set will be produced on ITT-R Set.

6 DEMOGRAPHICS AND OTHER BASELINE AND SCREENING CHARACTERISTICS

6.1 Demographics and baseline characteristics

Age will be calculated based on an assumed date of birth of January 1 for subjects who only have a year of birth based on region-specific regulations. Age will be calculated relative to the date of informed consent. Weight will be summarized from Visit 1 and body mass index (BMI) will be calculated using the subject weight recorded at Visit 1.

Age, age category 1 (18 to <65, 65 to <85, and ≥ 85 years), age category 2 (≤ 18 , 19 to <65, and ≥ 65 years), age category 3 (<17, 17 to <65, and ≥ 65 years), gender, CRF racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, not Hispanic or Latino), weight, height, BMI, categorized BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥ 40) will be summarized for the ITT-R Set.

Demographics listing will be provided on all subjects screened.

Time since first diagnosis (years), age at diagnosis (years), number of AEDs at study entry (see [Section 6.5.5](#)), LEV strata (Yes/No) and LEV use (Yes/No) at Visit 2 will be summarized in a separate table for ITT-R.

Time since first diagnosis (years) = Start Date of Epilepsy – Date of Randomization

Start date of Epilepsy should be taken from the CRF “Medical History” when the condition is Epilepsy.

Age at Diagnosis (years) = Start Date of Epilepsy – Date of Birth

6.2 Other screening characteristics

6.2.1 Seizure types for qualifying seizures observed during screening

The number and percentage of subjects experiencing each seizure type during the Screening Period after EMU admission prior to the study drug administration will be summarized for the ITT-R Set based on the data from the subjects’ seizure CRFs. The following ILAE classification of seizure types will be summarized: I, IA, IB, IC, II, IIA, IIA1, IIA2, IIB, IIC, IID, IIE, IIF and III.

Subjects will be counted for all higher levels of seizure type categories corresponding to the seizure types or seizure sub-types reported on the CRF. For example, subjects with an IA1 seizure will be counted for types I and IA.

Qualifying seizure is defined as: 1) the last seizure out of the ≥ 3 seizures per 24 hours occurred prior to the study drug administration, 2) the last seizure out of the ≥ 2 seizures in 6 hours occurred prior to the study drug administration or 3) the last seizure of one of the types IC, IC1, IC2, IC3, or IIE occurred prior to the study drug administration.

The summary of the type of the last qualifying seizure which triggers the study drug administration will be produced on ITT-R Set.

Shift tables summarizing the change from the last qualifying seizure at screening to next seizure event (see [Section 8.1.1](#)) during the Treatment Period will be provided on ITT-R Set based on the categories available from the CRF pages “Seizure Count” at Screening Visit 1 upon Admission and at Treatment Visit 2.

6.3 Medical and procedure history

6.3.1 Medical history

The number and percentage of subjects with a medical history condition not related to epilepsy, 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) for the ITT-R Set.

The medical history related to epilepsy (resolved and ongoing) at the time of study entry will be summarized by MedDRA primary SOC and PT for the ITT-R Set.

The listing of medical history glossary will be provided for the RS. Previous and ongoing medical history conditions listing will be provided on randomized set.

6.3.2 Procedure history

Prior medical procedures will not be summarized; medical procedures will only be provided in subject data listings.

6.4 Concomitant medical procedures

The listing of concomitant procedures recorded on the Concomitant Medical Procedures CRF will be provided for RS.

6.5 Prior and concomitant medications

Each medication recorded on the Prior and Concomitant Medication CRF will be classified as either an Anti-Epileptic Drug (AED) or a non-AED medication based on the coded Preferred Drug Name. Medications which pharmacologically can be classified as an AED but which were taken for non-epilepsy indications may also be classified as AEDs. The classification of such medications will be confirmed prior to database lock.

Prior and concomitant medications listings for AED and Non-AED separately will be provided on ITT-R. Outputs with glossaries of Non-AED medications and AED medications separately will be provided on ITT-R set.

6.5.1 Medications at study entry

Medications with the start date and time prior to or equal to the date of Visit 1 are considered medications at study entry.

6.5.2 Concomitant medications

Concomitant medications are medications taken at least one day in common with the study medication dosing period.

6.5.3 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 overall and by WHO-DRL pharmacological group (Anatomical Therapeutic Chemical [ATC] classification level 1), therapeutic subgroup (ATC classification level 2) and preferred drug name for the ITT-R Set. will be provided.

6.5.4 Concomitant Non-AEDs

The number and percentage of subjects taking concomitant non-AEDs will be summarized similar to non-AEDs at study entry for the ITT-R Set.

6.5.5 AEDs taken at study entry

The number and percentage of subjects taking AEDs at the time of study entry will be summarized by WHO-DRL preferred drug name for the ITT-R Set. The number and percentage

of subjects taking 0, 1, 2-4, and ≥ 5 AEDs taken at study entry will also be summarized for the ITT-R Set. The number and percentage of subjects stratified to LEV and taking LEV at Visit 2 will also be summarized for the ITT-R Set.

6.5.6 Concomitant AEDs

The number and percentage of subjects taking concomitant AEDs will be summarized by WHO-DRL preferred drug name for the ITT-R Set.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Dosing compliance will be evaluated through the review of important protocol deviations and will be summarized under important protocol deviations (see [Section 5.2](#)).

8 EFFICACY ANALYSES

8.1 Statistical analysis of the primary efficacy variable

Time to next seizure (per clinical observation with EEG confirmation) or rescue medication, representing treatment failure, from the end of study drug administration to 12 hours after the end of study drug administration will be compared between each BRV arm and LZP using survival analysis methods. All seizure data will be listed.

8.1.1 Primary efficacy variable

The primary efficacy variable is time to next seizure (per clinical observation with EEG confirmation) or rescue medication representing treatment failure, from the end of study drug administration to 12 hours after the end of study drug administration.

The event of next seizure is defined as the first seizure (clinically observed with the EEG confirmation) with the start date and time within 12 hours after the end of study drug administration.

The event of first rescue medication is defined as the first medication given to the subject during the study drug administration or within 12 hours after the end of study drug administration to suppress the qualifying seizure activity. If the first rescue medication is given on top of the study drug during the study drug administration, then the time to rescue medication will be set to 1 minute.

8.1.2 Derivations of primary efficacy variable

Time to next seizure (per clinical observation with EEG confirmation) or rescue medication from the end of study drug administration is defined as the minimum of:

- Start date and time of the next seizure minus end date and time of study drug administration.
- Start date and time of first rescue medication minus end date and time of study drug administration

Subjects are considered as censored if they do not have next seizure or first rescue medication events during the treatment period. Time to censoring is defined as the date and time of the end of the treatment period minus the end date and time of study drug administration. Subjects who discontinue the study without both events prior to the end of the treatment period are also censored and time to censoring is calculated as the date and time of last measurement during the treatment period minus the end date and time of study drug administration.

The primary efficacy variable is calculated in hours.

8.1.3 Primary analysis of the primary efficacy variable

Time to next seizure (per clinical observation with EEG confirmation) or rescue medication will be compared between each BRV arm and LZP and between combined BRV and LZP using log-rank test and Kaplan-Meier (KM) methods. The KM estimates at each hour during the 12 hours after the end of study drug administration, cumulative number of events, number at risk and median time to next seizure with 95% confidence interval and p-values from the log-rank test will be provided. KM curves will be plotted to compare the time to next seizure between each BRV and LZP and between combined BRV and LZP treatment groups. No adjustment for multiplicity will be made. Supporting statistical output will be provided for the primary analysis tables. If the sample size is sufficient, a subgroup analysis using strata (see [Section 4.8](#)) may be performed. The primary efficacy variable will be analyzed using ITT-R and PP sets.

8.1.4 Sensitivity analyses of the primary efficacy variable

If there are many subjects who discontinued with no data on seizure and/or rescue medication within 12 hours after the end of study drug administration, then the need for sensitivity analysis will be discussed at DEM and the statistical analysis plan will be updated to reflect any decisions. These subjects will be considered as subjects with events (next seizure/rescue medication) for the sensitivity analysis using ITT-R and PP sets.

8.2 Statistical analysis of the secondary efficacy variables

8.2.1 Time to next seizure or rescue medication

Time to next seizure or rescue medication is defined in the same way as the primary efficacy endpoint with the only difference that the seizure is clinically observed and not necessarily with EEG confirmation.

Time to next seizure (per clinical observation) or rescue medication from the end of study drug administration to 12 hours after the end of study drug administration will be analyzed similarly to the primary efficacy endpoint, i.e. compared between each BRV arm and LZP using log-rank test and KM curves using ITT-R and PP sets.

8.2.2 Seizure freedom at 6, 8 and 12 hours

Subjects are considered as seizure free if they do not have clinically observed seizures, have no interruption in seizure observation (the subject's seizure activity is continuously assessed over the next 12 hours following the end of study drug administration) and do not receive rescue medication.

Proportion of subjects seizure-free per clinical observation at 6 hours, 8 hours, and 12 hours after the end of study drug administration is defined as the number of subjects seizure free during 6, 8 and 12 hours after the end of study drug administration divided by the number of subjects in the ITT-R set. Subjects, who discontinued prior to 6, 8 and 12 hours after the end of study drug administration and therefore, their seizure data at 6, 8, and 12 hours are missing, are considered as if they had a seizure.

8.2.2.1 Analysis of the seizure freedom rates

Seizure freedom rates at 6 hours, 8 hours, and 12 hours after the end of study drug administration will be compared between each BRV arm and LZP using Fisher's Exact test. The p-values from the Fisher's Exact test are exploratory only, no adjustment for multiplicity will be performed.

The proportion of seizure-free subjects will be also analyzed using PP set with the same definitions only using subjects from PP set instead of ITT-R set.

8.2.3 Rescue medication during the 6, 8 and 12 hours

Rescue medication is given to subjects whose seizure activity continues after the end of study drug administration or requires additional medication on top of the study drug during the study drug administration, the start date and time of the rescue medication is after the end date and time of study drug administration. In cases when rescue medication was given during the study drug administration, it is set that the rescue medication is given 1 minute after the end of study drug administration.

Proportion of subjects with rescue medication during 6 hours, 8 hours, and 12 hours after the end of study drug administration is defined as the number of subjects who received rescue medication with start date and time within the first 6, 8, and 12 hours after the end of study drug administration divided by the number of subjects in the ITT-R set.

Subjects, who discontinued prior to 6, 8 and 12 hours after the end of study drug administration and therefore, their data on rescue medication at 6, 8, and 12 hours are missing, are considered as if they received rescue medication.

8.2.3.1 Analysis of rescue medication rates

Proportion of subjects who receive rescue medication during 6 hours, 8 hours, and 12 hours after the end of study drug administration will be compared between each BRV arm and LZP using Fisher's Exact test. The p-values from the Fisher's Exact test are exploratory only, no adjustment for multiplicity will be performed.

The proportion of subjects with rescue medication during the 6, 8, and 12 hours after the end of study drug administration will be also analyzed using PP set with the same definitions only using subjects from PP set instead of ITT-R set.

8.3 Analysis of other efficacy variable

8.3.1 Time to seizure resolution without additional intervention

This efficacy variable will be calculated only for subjects with ongoing seizures, i.e. actively seizing at the end of study drug administration.

The seizure is ongoing at the end of study drug administration if the seizure start date and time is before the end date and time of study drug administration and the seizure end date and time is after the end date and time of the study drug administration or is missing.

The event of seizure resolution without additional intervention is defined as the seizure started before the end date and time of study drug and stopped after the end date and time of the study drug administration without any rescue medication (see the definition of first rescue medication event [Section 8.1.1](#)).

The time to seizure resolution without additional intervention is defined as the end date and time of the seizure minus end date and time of the study drug administration.

If the ongoing seizure was not resolved without additional intervention and rescue medication (see [Section 8.1.1](#)) was given, then these subjects will be censored and time to censoring is the start date and time of the rescue medication minus end date and time of the study drug administration.

If the subject with the ongoing seizure discontinued and there is no data on the seizure resolution or rescue medication, then this subject will be considered censored and time to censoring is defined as the date and time of the end of the treatment period minus the end date and time of study drug administration.

8.3.2 Analysis of time to seizure resolution

Time to seizure resolution without additional intervention per clinical observation (only for the subjects actively seizing at the end of study drug administration) will be compared between each BRV arm and LZP using log-rank test and KM curves on ITT-R and PP sets.

Number of subjects with seizures resolved without additional intervention and not resolved will be summarized along with the median duration of time to resolution for the subjects who resolved without additional intervention. The summary will be produced for ITT-R and PP sets.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Summaries of clinical pharmacology will be limited to the plasma concentrations of BRV. No summaries of concomitant AED plasma levels will be provided. Data will be summarized for subjects in BRV treatment groups for the Pharmacokinetic Per-Protocol Set (PK-PPS).

Plasma concentrations of BRV are assessed at 1 hour and 5 hours after study drug administration for subjects who received BRV. Descriptive statistics for plasma concentrations of BRV will be provided by planned BRV dose per intake (ie. BRV 100mg or 200mg). Descriptive statistics will include the number of values, the number of values above the limit of quantification (LOQ), mean, SD, coefficient of variation, geometric mean, geometric SD, minimum value, and maximum value. Values below LOQ will be set to LOQ for all calculations.

Plasma sample collection times and plasma concentration listing will be provided on the PK-PPS.

9.2 Pharmacodynamics

Pharmacodynamics is not applicable this study.

10 SAFETY ANALYSES

Quantitative safety parameters will be summarized descriptively by time point. Categorical safety parameters will be summarized by the number and percentage of subjects within each category. Quantitative observed values and changes from baseline (pre-dose) in vital signs, and oxygen saturation will be summarized using continuous descriptive statistics. Assessment of cognitive impairment will be summarized in a similar way. All safety summaries by treatment group will be based on the ITT-T Set.

10.1 Study medication administration

All qualified subjects will receive a single iv dose of BRV 100mg, BRV 200mg, or LZIP. The data on study medication administration will be provided in subject data listings.

10.2 Adverse events

Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset on or after the start date and time of study drug administration.

10.2.1 General summaries of AEs

A table with overall summary of AEs will provide:

1. the numbers and percentages of subjects with any TEAE
2. the number and percentage of subjects with serious TEAEs
3. the number and percentage of subjects with non-serious TEAEs
4. the number and percentage of subjects with TEAEs leading to study discontinuation
5. the number and percentage of subjects with permanent withdrawal of study drug medication due to TEAEs
6. the number and percentage of subjects with a drug-related TEAEs
7. the number and percentage of subjects with a drug-related serious TEAEs
8. the number and percentage of subjects with severe TEAEs
9. the number and percentage of subjects with all deaths (AE leading to death)
10. The number and percentage of subjects with deaths (TEAEs leading to death)

The following tables - summaries of AEs will be provided by primary SOC and PT. Summaries will be presented by individual treatment groups and BRV total for the ITT-T Set.

- Incidence of pre-treatment AEs
- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of TEAEs by maximum intensity
- Incidence of drug-related TEAEs
- Incidence of drug-related serious TEAEs
- Incidence of serious TEAEs by relationship
- Incidence of fatal TEAEs by relationship
- Incidence of TEAEs leading to permanent discontinuation of study drug
- Incidence of non-serious TEAEs above reporting threshold of 5% of subjects in any treatment group

- **Incidence of TEAEs of Interest**

For the incidence of serious TEAE, TEAEs leading to permanent discontinuation of study drug and TEAEs of interest, the summary of subject numbers will be reported.

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 TEAEs within that SOC or PT. Severe intensity will be assumed for TEAEs for which intensity is not specified.

Drug-related TEAEs are TEAEs for which the relationship to trial medication is specified by the Investigator as Related or TEAEs for which relationship is not specified.

TEAEs of interest will be identified based on medical review. The incidence of TEAEs deemed to be of interest will be summarized by primary SOC and PT for the ITT-T Set.

All adverse events listing will be provided on screen failure subjects. All adverse events, serious adverse events, adverse events with fatal outcome, adverse events leading to permanent discontinuation of study drug, adverse events of interest listings will be provided on ITT-T set.

10.3 Clinical laboratory evaluations

No laboratory tests results are collected on the CRF in this study.

All parameters collected on the CRF "Laboratory Tests" will be provided only in subject data listings.

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

10.4.1 Vital signs and oxygen saturation

SBP (systolic blood pressure), DBP (diastolic blood pressure), and pulse rate are assessed at Visit 1 – Prior to randomization, Visit 2– Treatment and Visit 3 – Safety Follow-Up. For Visit 2 vital signs will be taken before dosing, end of bolus and at 5 min, 15 min, 30 min, 1 hour, 2 hours and 4 hours after end of bolus unless seizure or rescue medication occurs that ends the Treatment Period. If clinically significant abnormality is observed in the final assessment of the Treatment Period, the vital signs will be monitored every 4 hours until resolution or end of SFU Period. Body weight is assessed at Visit 1, Visit 2 and Visit 3. Height is assessed at Visit 1.

Observed values for SBP, DBP, and pulse rate will be summarized for each visit. Changes from Baseline for SBP, DBP, and pulse rate will be summarized for post-baseline visits and time points. Similar summaries will be provided for body weight.

The numbers and percentages of subjects with a PCST (possibly clinically significant treatment emergent) value, PCST low values, and PCST high value will be summarized for SBP, DBP, pulse rate, and body weight for Treatment and Safety Follow-Up Periods. For the PCST vital signs and body weight, the summary of subject numbers will be reported as well. PCST criteria are based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions and are included in the Appendices in the [Section 13.1](#).

Oxygen saturation is assessed at Visit 1 – Prior to randomization, Visit 2 – Treatment and Visit 3 – Safety Follow-Up. Observed values will be summarized for each visit. Changes from Baseline will be summarized for post-baseline visits and time points.

Line graph plots of observed vital sign parameters and oxygen saturation mean values and change from baseline in vital sign parameters and oxygen saturation mean values will be presented by visit and time point. Vital signs and oxygen saturation listing will be provided on ITT-T set.

10.4.2 Electrocardiograms

ECGs are performed at Visits 1 (Prior to randomization), 2 and 3 and may also be performed at unscheduled visits. No quantitative ECG parameters are collected on the CRF.

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, 2, and 3. Percentages will be relative to the number of subjects with an ECG at each 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 2, and 3 and Last Value (the latest available ECG measurement) will also be provided based on the categories normal and abnormal.

Last value is collected at the last subject visit.

ECG findings listing will be provided on ITT-T set.

10.4.3 Physical examination

A physical examination is performed at Visit 1 - Screening and may also be performed at Visit 2, Visit 3 and at unscheduled visits; findings are only recorded on the CRF at Visit 1. All physical examination data will be provided only in subject data listing.

10.4.4 Neurological examination

A neurological examination is performed at Visit 1 - Screening and may also be performed at Visit 2, Visit 3 and at unscheduled visits. All neurological examination data will be provided only in subject data listing.

10.4.5 Self-administered gerocognitive examination

The SAGE consists of a 22-point evaluation and is a handwritten self-test of memory developed to facilitate the screening of mild cognitive impairment and early dementia. The SAGE will be completed by the subject at Visit 1 – Prior to Randomization (Form 1) and at 1 hour (Form 2), 2 hours (Form 3), and 3 hours (Form 4) after the end of study drug administration. If study drug administration occurs for a nocturnal seizure and the subject is asleep, the SAGE should not be performed. SAGE score is calculated as the sum of individual scores from each item (see [Section 13.2](#)) SAGE score will be summarized by number of observations (n), mean, standard deviation, median, min and max for observed values at each visit and for change from baseline values at different timepoints of Visit 2, the baseline mean will also be displayed for change from baseline values. SAGE listing will be provided on ITT-T set.

11 BIOMARKER

Blood samples for epilepsy protein biomarker assay refinement will be collected at up to 4 time points after study drug administration: 1h (± 15 minutes), 5h (± 30 minutes), 12 (± 1) hours, and 24 (± 3) hours after the end of study drug administration.

Subject refusal of biomarker sample blood draws will not be considered a protocol deviation.

All information collected on CRF "Biomarker Sample" biomarker data will be provided only in subject data listing.

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12 REFERENCES

UCB Global Statistical Conventions, Version 1.1(27-Mar-2014)

Program Conventions Document: Brivaracetam, Version 1.1 (29-Sep-2016)

13 APPENDICES**13.1 Potentially clinically significant treatment-emergent criteria (PCST)****Introduction**

This document defines rules to be applied in the safety analyses of the UCB Pharma, Inc. clinical development programs in CNS Therapeutic Area. Rules for detecting possibly clinically significant treatment-emergent laboratory values, vital signs, and ECG parameters are considered. The purpose of this document is to bring consistency to reviewing laboratory data without over-riding the Investigator's clinical assessment of these parameters within the clinical context of the study subject.

POSSIBLY CLINICALLY SIGNIFICANT TREATMENT-EMERGENT (PCST) CRITERIA

Possibly clinically significant treatment-emergent (PCST) abnormal values are any treatment-concurrent laboratory values, vital signs, or ECG parameters meeting the criteria defined in this section. Treatment-emergent values are those occurring any time after screening and after the first dose of study drug have been taken. These PCST criteria will only be applied to data that was routinely collected.

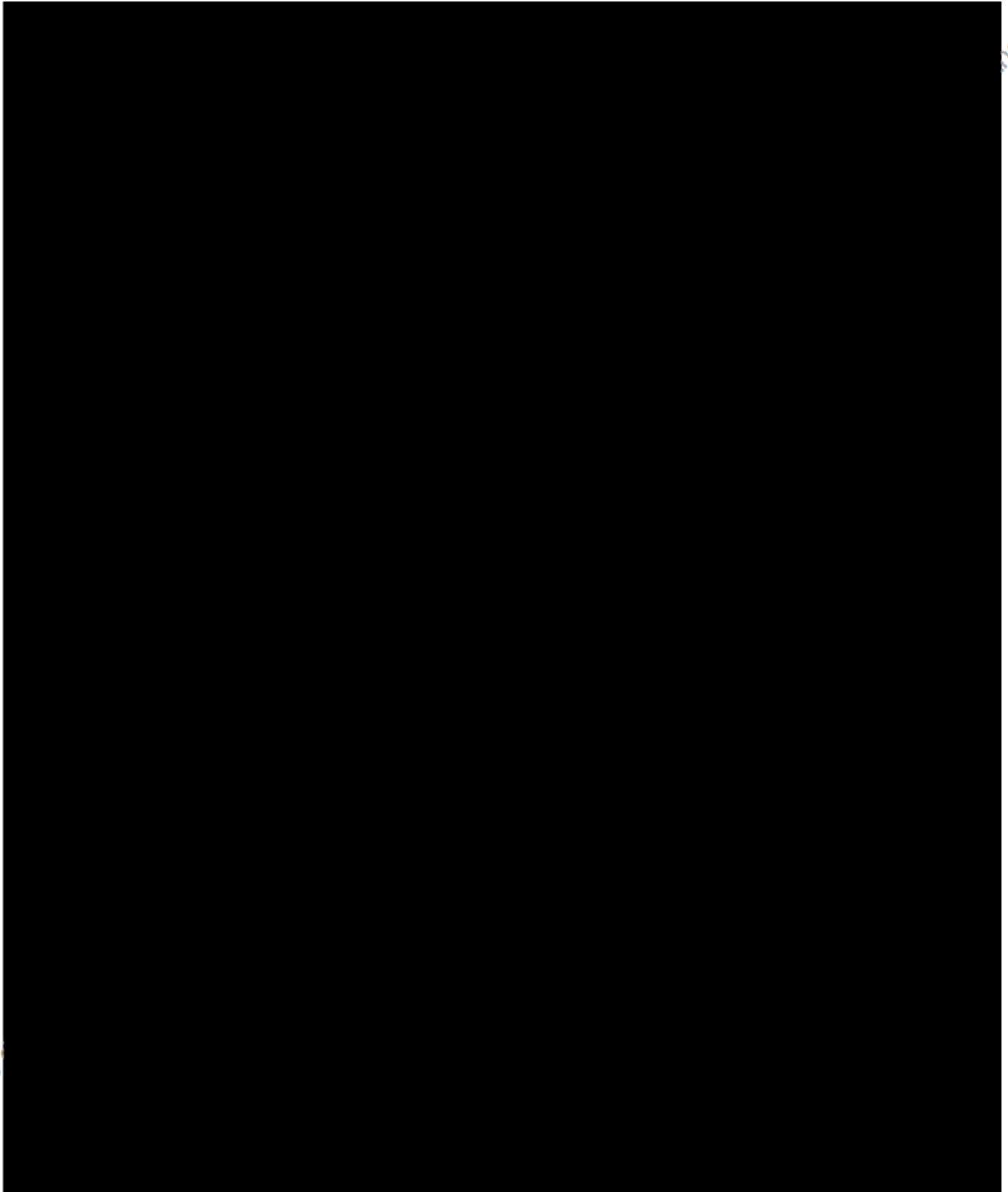
13.1.1 Vital signs and body weight

<i>PARAMETER</i>	<i>AGE RANGE</i>	<i>ABNORMALITY CRITERIA</i>
Pulse Rate (beats/minute)	<6m	<100 >180
	6m - <3y	<90 >150
	3y - <12y	<60 >130
	12y - <17y	<50 >120
	≥17y	<50 and a decrease from Baseline of ≥15 >120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
	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/>



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

14.1 Amendment 1

Global

Replaced “12 lead ECG” with “ECG”. “Upon admission” with “Prior to randomization”, “Preadmission” with “Screening”

Section 2.2.2

This section is new with Amendment 1.

Section 2.3

Original text:

Upon admission to the EMU, the subject will be randomly assigned (1:1:1) to receive a single iv dose of BRV 100mg, BRV 200mg, or LZP.

Study drug administration will begin when the Investigator or designee determines by clinical observation and EEG that a seizure requiring intervention (ie, qualifying seizure) has started. A qualifying seizure event is defined as:

- ≥ 3 seizures per 24 hours
- 2 seizures within 6 hours of each other
- Any generalized tonic-clonic seizure requiring intervention, as determined by the Investigator

The subject's seizure activity by clinical observation will be assessed over the next 12 hours following the end of study drug administration. In addition, the subject's cognitive impairment, vital signs, oxygen saturation, and ECG will be measured at specified time points.

If the subject is seizure-free for the 12 hours following the end of study drug administration, the Treatment Period is concluded and other AEDs may be administered at the Investigator's discretion. The subject is then in the Safety Follow-up (SFU) Period, which lasts until 24 hours after the end of study drug administration.

If the subject's seizure activity does not stop after administration of study drug or seizure activity recurs, the subject may receive rescue medication (not from study drug supplies) at the Investigator's discretion. At the time of rescue medication administration, the Treatment Period is concluded, and the subject is in the SFU Period.

The total duration of the study will be up to 4.5 weeks, inclusive of the Screening Period.

Screening Period (Visit 1 – Preadmission and Visit 1 – Upon Admission): lasts up to 28 days for consenting, planning EMU stay, randomization at the EMU admission, and inpatient EMU time prior to the seizure qualifying for study drug administration.

Treatment Period (Visit 2): beginning at start of study drug administration up to 12 hours following the end of study drug administration.

Safety Follow-Up Period (Visit 3): 24 hours following the end of study drug administration.

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

Updated text

Upon admission to the EMU and after screening, the subject will be randomly assigned (1:1:1) to receive a single iv dose of BRV 100mg, BRV 200mg, or LZP. The number of subjects using levetiracetam (LEV) as concomitant AED will be limited to 25% of the total number of subjects who receive study drug.

Study drug administration will begin when the Investigator or designee determines by clinical observation and EEG that a seizure requiring intervention (ie, qualifying seizure) has started. Study drug administration will begin within 30 minutes of the qualifying seizure. A qualifying seizure event is defined as any one of the following circumstances, requiring intervention in the opinion of the Investigator:

- ≥ 3 seizures per 24 hours
- ≥ 2 seizures in 6 hours
- Any generalized tonic-clonic seizure requiring intervention, as determined by the Investigator

The subject's seizure activity by clinical observation will be assessed over the next 12 hours following the end of study drug administration. The dose and regimen of concomitant AEDs should remain stable after study drug administration during the Treatment Period unless the subject needs rescue medication. In addition, the subject's cognitive impairment, vital signs, oxygen saturation, and ECG will be measured at specified time points. Blood samples will be obtained at specified time points.

If the subject is seizure-free for the 12 hours following the end of study drug administration, the Treatment Period is concluded and other AEDs may be administered at the Investigator's discretion. The subject is then in the Safety Follow-up (SFU) Period, which lasts until 24 hours after the end of study drug administration.

If the subject's seizure activity does not stop after administration of study drug or seizure activity recurs, the subject may receive rescue medication (not from study drug supplies) at the Investigator's discretion. At the time of rescue medication administration, the Treatment Period is concluded, the subject is in the SFU Period, and subject may be subsequently treated with AEDs at the discretion of the Investigator.

The total duration of the study will be up to 4.5 weeks, inclusive of the Screening Period.

Screening Period (Visit 1 – Screening and Visit 1 – Prior to randomization): lasts up to 28 days for consenting, planning EMU stay, randomization, and inpatient EMU time prior to the seizure qualifying for study drug administration.

Treatment Period (Visit 2): beginning at start of study drug administration up to 12 hours following the end of study drug administration.

Safety Follow-Up Period (Visit 3): 24 hours following the end of study drug administration.

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

Section 3.2.2.1

Original text

The Screening Period can start as early as on Day -28 until Day -1; it includes consenting, planning for EMU stay, randomization at the EMU admission, inpatient EMU time prior to the seizure qualifying for study drug administration. The Screening Period Visit 1 consists of two parts Visit 1 - Preadmission and Visit 1 - Upon Admission. Measurements with the date and time prior to the start date and time of study drug administration are in the Screening Period.

Updated text

The Screening Period can start as early as on Day -28 until Day -1; it includes consenting, planning for EMU stay, randomization, inpatient EMU time prior to the seizure qualifying for study drug administration. The Screening Period Visit 1 consists of two parts Visit 1 - Screening and Visit 1 - Prior to randomization. Measurements with the date and time prior to the start date and time of study drug administration are in the Screening Period.

Section 3.5.2

Removed the following from the end of the section:

The RS is also used for summaries of important protocol deviations.

Section 4.8

This section is new with Amendment 1.

Section 6.1

Original text

Age, age category 1 (18 to <65, 65 to <85, and ≥ 85 years), age category 2 (≤ 18 , 19 to <65, and ≥ 65 years), age category 3 (<17, 17 to <65, and ≥ 65 years), gender, CRF racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, not Hispanic or Latino), weight, height, BMI, and categorized BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥ 40) will be summarized for the ITT Set.

Updated text

Age, age category 1 (18 to <65, 65 to <85, and ≥ 85 years), age category 2 (≤ 18 , 19 to <65, and ≥ 65 years), age category 3 (<17, 17 to <65, and ≥ 65 years), gender, CRF racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other/Mixed), ethnicity (Hispanic or Latino, not Hispanic or Latino), weight, height, BMI, categorized BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥ 40) will be summarized for the ITT-R Set.

Time since first diagnosis (years), age at diagnosis (years) and LEV use (Yes/No) will be summarized in a separate table for ITT-R.

Time since first diagnosis (years) = Start Date of Epilepsy – Date of Randomization

Start date of Epilepsy should be taken from the CRF "Medical History" when the condition is Epilepsy.

Age at Diagnosis (years) = Start Date of Epilepsy – Date of Birth

Section 6.2.1

Added definition of qualifying seizure.

Added:

The summary of the type of the last qualifying seizure which triggers the study drug administration will be produced.

Section 6.4

This section is new with Amendment 1.

Section 8.1.3

The following was added:

If the sample size is sufficient, a subgroup analysis using strata (see [Section 4.8](#)) may be performed.

Section 9.1

This section is new with Amendment 1.

Section 10.2.1

Added the category for the TEAEs overview:

- the number and percentage of subjects with TEAEs leading to study discontinuation

Removed:

- Incidence of TEAEs by relationship
- Incidence of non-serious TEAEs by relationship
- Incidence of non-serious TEAEs above reporting threshold of 5% of subjects by relationship

Section 10.3

The following was removed:

Hematology, blood chemistry will have laboratory measures assessed at Visit 1 – Prior to randomization if laboratory evaluations have not been made in the previous 14 days and at Visit 3- Safety Follow-Up.

Added:

No laboratory tests results are collected on the CRF in this study.

Section 10.4.6

Added scoring algorithm

Section 11

This section is new with Amendment 1.

Section 13

Removed laboratory tests PCST criteria. Added SAGE scoring instructions.

14.2 Amendment 2

14.2.1 Rationale

Minor editorial changes were made throughout the document. Major changes are documented below.

Section 3.5.3, sentence 1, original text:

The Intent-to-Treat (ITT) Set will consist of all randomized subjects who received the study drug.

Updated text:

The Intent-to-Treat (ITT) Set will consist of all randomized subjects who received the study drug for qualifying seizures.

Section 6.1, paragraph 3, original text:

Time since first diagnosis (years), age at diagnosis (years), number of AEDs at study entry (see [Section 6.5.5](#)) and LEV use (Yes/No) will be summarized in a separate table for ITT-R.

Updated Text:

Time since first diagnosis (years), age at diagnosis (years), number of AEDs at study entry (see [Section 6.5.5](#)), LEV strata (Yes/No) and LEV use (Yes/No) at Visit 2 will be summarized in a separate table for ITT-R.

Section 6.2.1, paragraph 3, original text:

Qualifying seizure is defined as: 1) the last seizure out of the ≥ 3 seizures per 24 hours occurred prior to the study drug administration, 2) the last seizure out of the ≥ 2 seizures in 6 hours occurred prior to the study drug administration or 3) the last seizure of one of the types IC, IC1, IC2, IC3, II, IIA, IIA1, IIA2, IIB, IIC, IID, IIE or IIF occurred prior to the study drug administration.

Updated Text:

Qualifying seizure is defined as: 1) the last seizure out of the ≥ 3 seizures per 24 hours occurred prior to the study drug administration, 2) the last seizure out of the ≥ 2 seizures in 6 hours occurred prior to the study drug administration or 3) the last seizure of one of the types IC, IC1, IC2, IC3, or IIE occurred prior to the study drug administration.

Section 6.5.1, original text:

Medications with the start date and time prior or equal to the date of Visit 1 and the end date and time after the end date and time of study drug administration or marked as ongoing are considered medications at study entry.

Updated text:

Medications with the start date and time prior to or equal to the date of Visit 1 are considered medications at study entry.

Section 6.5.2, original text:

Medications that were taken during the treatment period regardless of the start and stop date and time are defined as concomitant medications.

Updated text:

Concomitant medications are medications taken at least one day in common with the study medication dosing period.

Section 6.5.5, original text:

The number and percentage of subjects taking AEDs at the time of study entry will be summarized by WHO-DRL preferred drug name for the ITT-R Set.

Updated Text:

The number and percentage of subjects taking AEDs at the time of study entry will be summarized by WHO-DRL preferred drug name for the ITT-R Set. The number and percentage of subjects taking 0, 1, 2-4, and ≥ 5 AEDs taken at study entry will also be summarized for the ITT-R Set. The number and percentage of subjects stratified to LEV and taking LEV at Visit 2 will also be summarized for the ITT-R Set.

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.

This document is not to be used to support any marketing authorisation application and any extensions or variations thereof.

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Approval Signatures

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