STATISTICAL ANALYSIS PLAN

Study: EP0085

Product: Brivaracetam

AN OPEN-LABEL, MULTICENTER, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN SUBJECTS ≥16 YEARS OF AGE WITH PARTIAL SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

SAP/Amendment Number	Date
Final SAP	26 SEP 2017
SAP Amendment 1	16 NOV 2021
SAP Amendment 2	17 JAN 2023
SAP Amendment 3	05 JUL 2023
SAP Amendment 4	03 FEB 2025

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AED	Antiepileptic Drug
BMI	Body Mass Index
BRV	Brivaracetam
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computerized Tomography
DEM	Data Evaluation Meeting
DRC	Daily Record Card
ECG	Electrocardiogram
EDV	Early Discontinuation Visit
EEG	Electroencephalogram
ES	Enrolled Set
FAS	Full Analysis Set
IMP	Investigational Medicinal Product
LTFU	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PCST	Possibly Clinically Significant Treatment-emergent
PDILI	Potential Drug-Induced Liver Injury
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
VNS	Vagus Nerve Stimulation
WHODD	World Health Organization Drug Dictionary
28DPSF	28-Day Adjusted Partial Seizure Frequency

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 4.1 and Case Report Form (CRF) version 8.0.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objectives

The primary objective is to evaluate the long-term safety and tolerability of BRV in focal epilepsy subjects with partial seizures.

2.1.2 Secondary objective

The secondary objective is to evaluate the maintenance of efficacy of BRV over time.

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

The primary safety variable is treatment-emergent adverse events (TEAEs).

2.2.1.2 Other safety variables

The other safety variables are as follows:

- Laboratory tests (blood chemistry, hematology, and urinalysis)
- Vital signs
- Body weight
- 12-lead electrocardiogram (ECG)
- Physical examination
- Neurological examination

2.2.2 Efficacy variables

The efficacy variables for rollover subjects in China and Japan include:

- Percent reduction in partial seizure frequency per 28 days from Baseline of EP0083 or N01358 to the Evaluation Period
- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥ 50% reduction in partial seizure frequency from the Baseline Period of EP0083 or N01358

Efficacy variables for direct enrollers in Japan include:

- Percent reduction in partial seizure frequency per 28 days from 8 weeks prior to BRV administration to the Evaluation Period

- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in partial seizure frequency from 8 weeks prior to BRV administration

Efficacy variables for all subjects (rollovers in China and Japan and direct enrollers in Japan):

- Percentage of subjects continuously seizure-free for partial seizures and all seizure types (partial, generalized and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

2.3 Study design and conduct

EP0085 is a Phase 3, open-label, long-term follow-up (LTFU), multicenter, noncomparative, and dose flexible study being conducted in Japan and China. The population are subjects (≥16 years of age) with partial seizures with or without secondary generalization. Subjects of a minor age are included only where legally permitted and ethically accepted. In Japan, subjects meeting the inclusion and exclusion criteria as specified in the study protocol can be directly enrolled. Rollover subjects must complete the Treatment and Transition Period of EP0083 prior to enrolment into EP0085. In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Directly enrolled subjects in Japan will have their eligibility confirmed at the Screening Visit (SV). SV occurs -2 to -21 days before BRV administration. Directly enrolled subjects in Japan and rollover subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment.

Subjects from N01379 can enter EP0085 at a dose up to 200mg/day. After Visit 1, the next visit for subjects entering from N01379 will be Visit 4 (Visit 2 and Visit 3 will not be conducted). Subsequent visits will be conducted according to the visit schedule according to EP0085 study protocol. (see Table 1). The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered as a symmetrical morning and evening dose except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study drug in the last week of down-titration is given only in the morning.

The study duration per subject is defined as follows:

- Screening Visit (Visit 0, up to 3 weeks before the Entry Visit (EV) for direct enrollers in Japan only)
- Evaluation Period (Visit 1 to End of Study Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in EP0083 and N01379 will enter the Evaluation Period
- Down-Titration Period (up to 4 weeks):

- If the subject is discontinuing study drug, the Investigator will first plan an EDV followed by the progressive down-titration of study drug.
- During the Down-Titration 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 for 1 week should be included prior to the 2-week Study Drug-Free Period.

- 2-week Study Drug-Free Period: After completion of the Down-Titration Period, or for those subjects who for extenuating circumstances do not complete a Down-Titration Period, the subject will be required to enter a 2-week Study Drug-Free Period, followed by a Final Visit (FV).

Subjects who will be converted to the commercial BRV product will complete an End of Study Visit without entering the Down-Titration Period or the 2-week Study Drug-Free Period and will not complete an FV.

Visits should occur on the specified Visit/Week. A ±7 day 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.

EP0085 will continue until the market approval of BRV, or until the sponsor decides to close the study, whichever comes first. In the event that market approval is not requested or obtained in the participant country, the subject will be able to continue in EP0085 for two years after entering EP0085.

In Japan, EP0085 will continue as a postmarketing clinical study (Phase 4) after the date of approval of BRV for the partial seizure indication.

At selected sites in Japan, Japanese subjects may participate in an additional study (EP0118) with the intravenous formulation of BRV without withdrawing from EP0085. Ten evaluable subjects are planned for EP0118, and the total duration in the study for each subject is 7 days. The study period of EP0118 will be included in that of EP0085. Subjects will continue to receive their current dose of BRV at the time of entry and it will remain stable for the duration of EP0118. Subjects who complete or withdraw from EP0118 will resume their participation in EP0085 with oral BRV treatment. In the event that a subject withdraws from EP0118 and is required to down-titrate BRV treatment, the subject will return to EP0085 and down-titrate using BRV tablets. TEAEs and concomitant treatment(s)/medication(s) that occur or are administered during EP0118 will be recorded in EP0118. Ongoing TEAEs and concomitant medication(s)/medical procedure(s) originating from EP0118 will be recorded and followed in EP0085 until resolution or until the status of the TEAE and/or concomitant medications are stable. All other data reported for EP0118 will be captured in the EP0118 database. Per the EP0118 protocol, the study (EP0118) will require hospitalization. Hospitalization for study participation does not need to be reported as an SAE.

Table 1: Full visit schedule

First year follow-up		
Month (Week)	**Visit**	**Type of visit**
-2 to -21 days	V0	SV[a]
M0 (W0)	V1	EV
M1 (W4)	V2[c]	MEV[b]
M2 (W8)	V3[c]	FEV
M3 (W12)	V4	MEV[b]
M4 (W16)	-	-
M5 (W20)	-	-
M6 (W24)	V5	FEV
M7 (W28)	-	-
M8 (W32)	-	-
M9 (W36)	V6	MEV[b]
M10 (W40)	-	-
M11 (W44)	-	-
M12 (W48)	V7	YEV
Second year follow-up [c]		
Month	**Visit**	**Type of visit**
M15 (W60)	V8	MEV[b]
M18 (W72)	V9	FEV
M21 (W84)	V10	MEV[b]
M24 (W96)	V11	YEV

EV=Entry Visit; FEV=Full Evaluation Visit; M=month; MEV=Minimal Evaluation Visit; SV=Screening Visit; V=Visit; W=Week; YEV=Yearly Evaluation Visit

Note: A dash (-) denotes that no visit is scheduled in that month.

[a] For subjects directly enrolled into EP0085 in Japan only.

[b] Laboratory safety assessments will not be performed at MEV. Only liver function tests will be performed at MEV in the first year (V4 and V6).

[c] Subsequent years will follow the same visit schedule.

2.4 Determination of sample size

For this open-label LTFU study, no sample size calculation was performed. The sample size will depend upon recruitment into and completion of the previous studies. Overall, approximately 217 subjects are planned for enrollment. In Japan, it is estimated that approximately 127 subjects will enter the study. This estimate assumes that at least 90% of randomized Japanese subjects will complete EP0083 (approximately 90 subjects) or enroll from N01379 sites in Japan (7 subjects) and that 30 Japanese subjects will be directly enrolled in this study. Likewise, this estimate assumes that at least 90% of randomized Chinese subjects will complete EP0083 (approximately 90 subjects).

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

For the analysis purposes, "core study" in this plan refers to the study where the subjects were firstly enrolled. For rollover subjects, the core study is N01358 (for rollover subjects from N01379) or EP0083 (for rollover subjects from EP0083). For direct enrollers EP0085 is the core study.

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS® Version 9.3 or higher.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

For continuous parameters, descriptive statistics will include number of subjects with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum. Decimal places for descriptive statistics will always apply the following rules:

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

All summaries will be descriptive; no statistical hypothesis testing is planned.

Subject data listings will be provided and will present source data and key derived variables for statistical analyses.

3.2 Analysis time points

3.2.1 First and last dose of BRV

Unless otherwise noted, all references to the first dose of BRV in this SAP refer to the first dose of BRV during EP0085 (ie, not the first dose of BRV from the previous study in which subjects participated in prior to EP0085). Unless otherwise noted, all references to the last

known dose of BRV in this SAP refer to the last dose of BRV taken across any study periods (ie, the last dose of BRV across both the Evaluation and Down-Titration Periods).

3.2.2 Relative day

Relative day will be calculated as follows:

- For days prior to the first dose of BRV, the relative day is the current date minus the date of first dose of BRV. The relative day prior to first dose will be Day -1.
- For days on or after the first dose of BRV and on or prior to the last dose of BRV, the relative day is the current date minus the date of first dose of BRV plus 1. The relative day of first dose will be Day 1.
- For days after the last dose of BRV, the relative day is the current date minus the date of last dose of BRV. The relative day 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 or missing dates.

3.2.3 Screening Visit

The SV only applies to direct enrollers in Japan and will be performed between Day -21 and Day -2 prior to Visit 1 (EV). The following assessments will be performed at SV:

Study	Visit	Assessments
EP0085 direct enrollers in Japan	Visit 0	Demography, medical history, epilepsy history, AED history, vital signs, body weight, physical examination, neurological examination, 12-lead ECG, electroencephalogram (EEG), neuro-imaging procedure (per Investigator discretion), laboratory safety assessments, seizure counts, ongoing AE reporting (see more information in Section 9.2), C-SSRS, medical procedures, ongoing concomitant medications (including AEDs and non-AEDS).

3.2.4 Entry Visit

The EV corresponds to the assessments performed at the time of entry into EP0085. For direct enrollers in Japan, the EV will be performed at Visit 1 and the relevant assessments will be performed according to the study protocol. For rollover subjects from EP0083 and N01379, the following assessments will be completed during the last visit of the previous study and do not need to be repeated at Visit 1:

Study	Visit	Assessments
EP0083	Visit 8	vital signs, body weight, physical examination, neurological examination, 12-lead ECG, laboratory safety assessments, seizure counts, ongoing AE reporting (see more information in
N01379	Last Evaluation Period Visit or Early Discontinuation Visit	

		Section 9.2), C-SSRS, medical procedures, ongoing concomitant medications (including AEDs and non-AEDS).

3.2.5 Study periods

The following study periods are defined for the classification in summary that are based on the study design:

Baseline Period	For rollover subjects from EP0083, the Baseline Period corresponds to the Baseline Period of EP0083 and is defined as study days on or after EP0083 Visit 1 date and prior to EP0083 Visit 3 date. For rollover subjects from N01379, the Baseline Period corresponds to the Baseline Period of N01379 and is defined as study days on or after N01358 Visit 1 date and prior to N01358 Visit 3 date. For direct enrollers, except for seizure outcome the Baseline Period is defined as study days on or after EP0085 Visit 0 date and prior to EP0085 Visit 1 date. The Baseline Period for seizure outcome is defined as 8 weeks prior to the first BRV administration (see section 8.1.2).
Evaluation Period	The Evaluation Period starts on the date of Visit 1 and the following algorithm is used to determine the end date: If the subjects enter the Down-Titration Period: - for completed subjects, which is indicated by the CRF "Study Termination" form (Complete subject), the Evaluation Period ends on the date of End of Study Visit date. - for discontinued subjects, which is indicated by the CRF "Study Termination" form (Dropout), the Evaluation Period ends on the date of EDV date. If the subjects do not enter the Down-Titration Period: For complete / discontinued subjects who do not enter the Down-Titration Period, the end of Evaluation Period will be the date of last dose of BRV.
Down-Titration Period (up to 4 weeks)	If the subject is discontinuing BRV, the Investigator will first plan an EDV followed by the progressive down-titration of study drug.

	A subject is considered entering Down-Titration Period only if the subject has an EDV and has at least 1 dose of study drug after the date of EDV, the start date of Down-Titration Period is set as 1 day after the date of EDV, and the Down-Titration Period ends on date of last dose of BRV. A subject without an EDV but having a termination CRF or with an EDV but without any dosing of study drug after the EDV will not have the Down-Titration Period, and no artificial Down-Titration Period will be created for analysis.
Study Drug-Free Period (2 weeks)	After completion of the Down-Titration Period, or for those subjects who for extenuating circumstances do not complete a Down-Titration Period, the subject will enter a 2-week Study Drug-Free Period, followed by a Final Visit. A subject is considered entering the Study Drug-Free Period if the subject has at least 1 contact (scheduled visit, unscheduled visit, or telephone contact) after the date of last dose of BRV. The 2-week Study Drug-Free Period starts 1 day after the date of last dose of BRV and ends on the date of Final Visit, irrespective of entering the Down-Titration Period.

A subject is considered as completed if this subject completes all scheduled visits as defined in the protocol or converts to commercial BRV without a Down-Titration Period (where commercial BRV is available).

3.2.6 Monthly time intervals

In terms of the analysis, a month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days). The following definitions of 3-month intervals are based on 30-day months where the date of first dose of BRV is Day 1:

Interval	Duration Definition
3-month interval	
Month 1-3	Day 1-90
Month 4-6	Day 91-180
Month 7-9	Day 181-270
Month 10-12	Day 271-360

Subsequent 3-month intervals are defined in a similar manner. Three-month intervals will be used for analyses of efficacy (except for continuously seizure-free) and TEAE summaries.

For the analysis of efficacy outcomes, a subject is included in the analysis of a 3-month interval if the last dose of study drug during the Evaluation Period of EP0085 is equal or

greater than the last day of the 3-month time interval and the seizure diary was completed for at least 1 day during the 3-month interval over the Evaluation Period.

For TEAE summaries, a subject is included in the analysis of a 3-month interval if the last dose of study drug in whole period of EP0085 is equal or greater than the first day of the 3-month time interval (as N for the time interval) and with at least one specified TEAE within the 3-month interval (as n in the summary tables according to the AE onset date).

3.2.7 Last Value on BRV Treatment

Last Value for clinical laboratory parameters, vital signs, and ECGs is the last available result obtained after the first dose of BRV and prior to or on the date of last dose of BRV. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each laboratory parameter.

3.3 Definition of Baseline values

Unless otherwise specified, Baseline for all safety and efficacy variables will be based on baseline of the core study.

For rollover subjects, the baseline value for all safety and efficacy variables is defined as the last non-missing data collected prior to the first dose of study medication in the core study (EP0083 or N01358), unless addressed otherwise for a specific type of data. Baseline seizure frequency will be obtained from the core study (EP0083 or N01358).

For direct enrollers in Japan, the baseline value is defined as the last non-missing data collected prior to the first dose of study medication in study EP0085, unless addressed otherwise. For seizure frequency, the baseline is defined as the seizure counts collected from 8 weeks prior to the first BRV administration. This baseline seizure frequency for direct enrollers is consisted of subject's own document (eg, DRC) and the data in DRC for EP0085 between SV and EV.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the evaluation of safety and efficacy outcome. Protocol deviations will be identified during ongoing data monitoring and cleaning process and will be reviewed in the Data Cleaning Meetings. The impact of the protocol deviations to the analysis will be discussed in Data Evaluation Meeting.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of subjects who signed an informed consent form in EP0085, enrolling from study EP0083 or from study N01379 or are directly enrolled into EP0085 in Japan. This analysis set is also referred to as “All Subjects Screened”.

3.5.2 Safety Set

The Safety Set (SS) will consist of all subjects in the ES who took at least 1 dose of study medication in EP0085. All safety variables will use SS for presentation. In addition,

demographic data, baseline characteristics, medical history, prior and concomitant medications and study drug exposure will use SS for presentation as well.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the ES who took at least 1 dose of study medication and have at least 1 seizure record on Daily Record Card (DRC) during the Evaluation Period. All efficacy variables will use FAS for presentation.

3.6 Treatment assignment and study groups

This is an uncontrolled study in which all subjects receive BRV in doses that are optimally adjusted for each subject. It is expected that subjects will receive treatment in accordance with the study design.

Rollover subjects from N01379, EP0083, and directly enrolled subjects need to be analyzed separately. For rollovers from EP0083 a detailed segmentation by randomized drug group in EP0083 is necessary. Unless otherwise specified, results will be presented for each grouping described below:

For tables and figures the study groups will be presented as follows:

- EP0083 Placebo
- EP0083 BRV All
- EP0083 Total
- N01379
- Direct Enrollers
- All Subjects

For subject listings, the study group will be presented as follows:

- EP0083 Placebo
- EP0083 BRV 50mg/day
- EP0083 BRV 200mg/day
- N01379
- Direct Enrollers

For submission purpose, the subgroup tables and figures will be presented by Japan. In Japan subgroup tables and figures, the study groups will be presented in the same manner as overall.

3.7 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD) version September 2017. Medical procedures or medical devices will not be coded.

3.8 Changes to protocol-defined analyses

Not applicable.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Handling of missing data

No rule for handling of missing data will be applied for this LTFU study. Safety and efficacy variables will be analyzed as available. Days with missing information will be ignored in the calculation of the seizure frequency.

Since subjects may drop out from the study at different times, selected summaries will be presented by time interval.

Subjects participating in EP0118 while also enrolled in EP0085 will have missing data for seizure frequency and drug dosing while participating in the EP0118 study. As the duration of the EP0118 study will be short (3-7 days), no imputation for data missing due to participation in EP0118 will be performed. Subjects will be assigned the same dose in EP0118 as that assigned in EP0085 for the two weeks prior to the start of EP0118. As such, time during the EP0118 study will not be subtracted from the exposure calculations (eg, exposure will be from the start of BRV treatment in the EP0085 study until the date of last dose of BRV in EP0085).
For the calculation of variables related to seizure frequency, the dates during participation in EP0118 will be considered as not done for the purpose of efficacy analyses for EP0085 according to the Seizure Count form entry (eg, these dates will not be considered as days evaluated for seizure frequency).

4.2 Interim analyses and data monitoring

No formal interim analysis is planned. However, data will be reported prior to the completion of this study to support regulatory submissions. At a minimum, 2 interim reports are planned after all ongoing subjects have completed Visit 5 (Week 24) and after all ongoing subjects have completed Visit 7 (Week 48). There are no statistical concerns with such interim reports for this open-label LTFU study.

4.3 Multicenter studies

The disposition of subject by study center will present in the summary table by study center. The information of study centers will also be identified in the Subject Disposition listing. Efficacy and safety outcomes will not be assessed for individual study center due to the low expected number for enrollment within each study center.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of screen failures and the primary reason for screen failure will be summarized for all subjects screened. The number and percentage of subjects who started, completed and discontinued will be presented by study period, 6-month periods over the Evaluation Period and study group.

The number of subjects by site will be provided in a separate summary table for the ES. The number and percentage of subjects in different analysis sets will be provided based on the ES. The summary of subjects in the SS who discontinued the study due to AE will be presented in a separate table.

All subject disposition related information and subjects who did not meet the inclusion/exclusion criteria will be provided in the subject listings.

5.2 Protocol deviations

The number and percentage of subjects with at least one important protocol deviation will be summarized by main category of protocol deviation by study group. The percentage will be based on the Safety Set.

The assignment of subjects to each of the analysis sets will be listed for all subjects enrolled.

5.3 Consideration for COVID-19

A new Coronavirus Disease 2019 (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 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 to describe the impact of COVID-19 will be performed. AE related to COVID-19 vaccination will be flagged in the AE listings (see section 9.2.2.8).

5.4 Time to BRV discontinuation

As an additional assessment, the time to BRV discontinuation will be evaluated for both the overall study population and the Japanese subpopulation.

The time to BRV discontinuation will be calculated as follows:

(Date of last dose of BRV – date of first dose of BRV +1) / 30 (in month)

The time to BRV discontinuation will be analyzed using Kaplan-Meier method. The median time, 25% percentile, and 75% percentile of time to BRV discontinuation will be calculated based on SS. Additionally, the cumulative number of events, number at risk, and survival estimate at month 12, 24, 36, 48, 60, 72, 84, and 96 will be provided.

Subjects who discontinued BRV for any reason will be considered as an event. All other subjects will be censored at the date of the last dose of BRV.

In addition to analyzing BRV discontinuation due to any reason, the time to BRV discontinuation will be separately analyzed for the following specific reasons:

- Due to TEAE
- Due to lack of efficacy
- Due to lack of efficacy or TEAE

For each of the BRV discontinuation reason, a summary table will be provided by study group. Additionally, a Kaplan-Meier figure will be provided combing all discontinuation reasons and presented, by study group.

6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All summaries for subject characteristics will be based on SS. Unless otherwise specified, all demographics and other baseline characteristics summaries will be based on data collected in the core study.

6.1 Demographics

Age, age category, gender, racial group, ethnicity, ethnicity subgroup (Japan or China), body weight (kg), height (cm), body mass index (BMI) (kg/m^2), and BMI category will be summarized by study group for the Safety Set.

The age will be categorized according to the following categories:

- 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
- clinicaltrials.gov: ≤18, 19 to <65 and ≥65 years

The BMI will be categorized according to the following category:

- <18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40

Age will be calculated based on the date of informed consent in EP0085 and date of birth. The result will be kept as integer and the unit of age is years. A birth date of each subject provided from the core studies is imputed to be born on the first day of that month (yyyy-mm-01). Except for age, all other demographic variables will be based on data from baseline of core study.

The demographic variables will be listed by subject.

6.2 History of epilepsy

The following epilepsy-related background variables will be summarized by study group based on the Safety Set:

- Epileptic seizure profile: the number and percentage of subjects experiencing each seizure type at any time based on the Classification of Epileptic Seizures (ILAE,1981) prior to the core study entry will be summarized.
- History of epileptic seizures at the core study: the number and percentage of subjects with a history of status epilepticus and quantitative summaries of epilepsy duration, age at time of first diagnosis of seizure, and percent of life with epilepsy, will be summarized. Percent of life with epilepsy will be calculated as 100 times epilepsy duration relative to the first diagnosis date and divided by the subject's age at the core study entry.

- Classification of epileptic syndrome collected at the core study: the number and percentage of subjects with each epileptic syndrome will be summarized.
- Baseline seizure type and partial seizure frequency collected at the core study: the number and percentage of subjects who experienced each seizure type during the Baseline Period of core study will be presented. 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 of core study.

For rollover subjects, the data will be obtained from the Baseline Period of N01358 and EP0083. For direct enrollers, the data will be obtained from EP0085 Screening Visit CRF forms.

All above-mentioned baseline characteristics will be listed by subject.

6.3 Medical history conditions and procedure history

For rollover subjects, the medical history conditions and procedure history will be obtained directly from the Medical History CRFs and the Procedure History CRFs of the EP0083 and N01358 (for rollover subjects from N01379). If there is any new medical history condition, it will be collected in the Medical History Update form in EP0085. For direct enrollers, the medical history conditions and procedure history will be obtained from the Medical History CRFs and the Procedure History CRFs of EP0085. Reported medical history conditions are coded according with MedDRA version 18.1. Medical procedures are not coded. Start and stop date are documented partially with month and year only (yyyy-mm). No date imputation is foreseen.

6.3.1 Previous and ongoing medical history conditions

The number and percentage of subjects with a medical history condition, including both resolved and ongoing conditions, will be summarized by study group by the primary System Organ Class (SOC) and Preferred Term (PT).

A listing of subjects with previous and ongoing medical history conditions will be provided.

6.3.2 Procedure history and concomitant procedures

A listing of subjects with procedure history and concomitant procedures will be provided.

6.4 Prior and concomitant medications

All prior and concomitant medications will be coded according to the WHODD version September 2017. Medications taken at study entry are the ongoing medications at the study entry of the core study. Previous medications are medications taken and discontinued prior to entry into the core study. Concomitant medications are medications taken during administration of BRV in EP0085 study. Previous AEDs and AED taken at core study entry will follow the AED definition according to the respective core study.

6.4.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AEDs at study entry will be summarized for the Safety Set by primary therapeutic group (Anatomic Therapeutic Class [ATC] level 1), therapeutic subgroup (ATC level 2), and preferred drug name.

Non-AED taken at study entry refers to the core study entry. The non-AEDs at core study entry will follow the AED definition according to the respective core study. For rollover subjects the information will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications" from N01358 (for subjects from N01379). For direct enrollers the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

6.4.2 History of previous AED use

The number and percentage of subjects who had taken at least 1 previous AED prior to entry into the core study will be summarized overall and by preferred drug name for the Safety Set. For rollover subjects the information will be obtained from CRF form "History of Previous Antiepileptic Drug Treatment" from EP0083 and N01358 (for subjects from N01379). For direct enrollers the information will be obtained from EP0085 CRF form "History of Previous Antiepileptic Drug Treatment". Different with the core study N01358, for core study EP0083 (for the rollover subjects from EP0083) and EP0085 (for the direct enrollers), the history of previous AED was recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol, however, the Investigator's judgement was prioritized and taken into consideration.

6.4.3 Number of previous AEDs

The number and percentage of previous AEDs will be summarized based on the following categorization: 0-1 AEDs, 2-4 AEDs, and ≥5 AEDs. The definition of previous AED use will be the same as section 6.4.2.

6.4.4 AEDs taken at study entry

The number and percentage of subjects taking AEDs at the core study entry visit will be summarized by preferred drug name for the Safety Set.

AED taken at study entry refers to the core study entry. The AEDs at core study entry will follow the AED definition according to the respective core study. Different with the core study N01358, for core study EP0083 (for the rollover subjects from EP0083) and EP0085 (for the direct enrollers), the AEDs taken at study entry was recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol and was captured according to the CRF "Core AED?" based on the Investigator's judgement.

For rollover subjects the information will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications (AEDs only)" from N01358 (for subjects from N01379). For direct enrollers the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

6.4.5 Concomitant AEDs

A concomitant AED is an AED which was taken during administration of BRV in EP0085 study, regardless of the start and stop date of the AED. Concomitant AEDs 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. The

number and percentage of subjects taking concomitant AEDs will be summarized by preferred drug name for the Safety Set.

6.4.6 Vagus nerve stimulation (VNS)

For all subjects, the VNS information will be obtained from EP0085 CRF form: Vagus Nerve Stimulation Status at Screening/Baseline. The number and percentage of subject who had VNS at Screening/Baseline of EP0085 will be summarized in a table. A listing of VNS status at study entry and VNS setting at the subsequent visits will be provided.

6.5 Potential drug-induced liver injury (PDILI) related information

Subjects with potential drug-induced liver injury (PDILI) will be assessed to determine if IMP must be discontinued. If PDILI occurs, additional lifestyle and family medical history information will be collected. Listings of lifestyle and family medical history will be provided only if any subject reporting PDILI.

6.6 Neuro-imaging procedure

A neuro-imaging procedure, including brain magnetic resonance imaging (MRI), brain computerized tomography (CT) scan or other imaging test will be performed for direct enrollers at Screening Visit per Investigator discretion. A listing of CT and MRI data will be provided.

6.7 Electroencephalogram

For direct enrollers, if there is no appropriate EEG available within the last 10 years, a Baseline EEG must be scheduled at the SV and the results received before the EV. A listing of EEG interpretation data will be provided.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug compliance will not be calculated because the planned dose information is not collected and also due to the complexity associated with the interpretation of study drug compliance for this study. However, study drug compliance will be evaluated during the review of important protocol deviation. Study drug dosing will be provided in subject data listings.

8 EFFICACY ANALYSES

All efficacy outcomes will be summarized with descriptive statistics only on the FAS. All efficacy analyses to the Evaluation Period will be based on the seizure records during the Evaluation Period on/after the first dose of BRV.

8.1 Derivations of efficacy variable(s)

The derivation and definition of efficacy variables in this study are addressed in this section.

8.1.1 28-day adjusted seizure frequency

The 28-Day Adjusted Partial Seizure Frequency (28DPSF) will be calculated by dividing the number of partial seizures by the number of days for which the DRC was completed and multiplying by 28, eg, as following equation:

$$28\text{DPSF} = \frac{\text{Number of partial seizures}}{\text{Number of days completed in the DRC}} \times 28$$

For the 28-day adjusted frequency of all seizure types (partial, generalized and unclassified epileptic seizure), the number of numerator will include partial, generalized and unclassified epileptic seizure.

8.1.2 Percent reduction of 28-day adjusted partial seizure frequency

Percent reduction of 28DPSF from Baseline is defined as the percentage reduction of 28DPSF for a designated post-baseline period in EP0085 compared with the Baseline 28DPSF in the core study. This variable will be derived as following equation:

$$\text{Percent reduction} = \frac{\text{Baseline 28DPSF} - \text{Post Baseline 28DPSF}}{\text{Baseline 28DPSF}} \times 100$$

For rollover subjects the Baseline seizure will be obtained from EP0083 and N01358 study. For direct enrollers, the Baseline seizure counts will be collected from 8 weeks prior to the first BRV administration (see section 3.3) and the number of days during the Baseline Period will be set as 56 days.

8.1.3 Responder rate of 28DPSF

A responder is defined as a subject with a ≥50% reduction of 28DPSF from the Baseline to the designated period.

8.1.4 Seizure freedom (partial, all epileptic seizure)

A subject is defined as seizure free for a designated period during the Evaluation Period if they meet **all of** the following criteria:

- Criteria 1: the subject completed the designated period during the Evaluation Period
- Criteria 2: the subject has at least 90% non-missing diary days during the period of time
- Criteria 3: the subject did not report any seizures during the period

8.2 Analysis of the efficacy variables

8.2.1 Analysis of seizure frequency per 28 day

Based on the definition in the Section 8.1.1, the partial seizure and all type seizures frequency per 28 days will be summarized by descriptive statistics for continuous parameters by study group. The analysis time intervals will be 3-month periods over the Evaluation Period. In addition, the partial seizure and all type seizures frequencies per 28 days all over the Evaluation Period will be summarized in the same way.

8.2.2 Analysis of percent reduction of 28DPSF

The percent reduction of 28DPSF from Baseline will be summarized by descriptive statistics as continuous parameters (refer to the Section 3.1) by study group. The analysis time intervals will be 3-month periods over the Evaluation Period. In addition, the percent reduction of 28DPSF all over the Evaluation Period will be summarized in the same way.

8.2.3 Analysis for responder rate of 28DPSF

The number and percentage of responders will be summarized by study group. The analysis time intervals will be 3-month periods over the Evaluation Period. The denominator of percentage will be based on the total number of subjects with at least 1 seizure assessment during the time interval. The numerator will be the number of responders.

8.2.4 Analysis of seizure freedom

Based on the definition of seizure free in the Section 8.1.4, the parameters in the following sub-sections will be analyzed respectively.

8.2.4.1 The percentage of subjects continuously seizure-free

The number and percentage of subjects who have been continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period will be summarized.

In addition to the 6 months and 12 months of intervals of continuously seizure-free, subsequent 6-month intervals will be summarized in a similar manner.

The percentage of subjects with continuously seizure-free will be based on the number of subjects exposed to BRV for at least the specific time interval.

8.2.4.2 Seizure Freedom

The number and percentage of subjects with seizure-freedom (partial, all epileptic seizure) during the Evaluation Period will be summarized by study group.

9 SAFETY ANALYSES

All safety analysis will be based on SS.

9.1 Extent of exposure

9.1.1 Study medication duration and total study medication duration in subject-years

Duration of exposure to study medication is defined as the total number of days a subject is exposed to study medication and will be calculated as the date of last dose in EP0085 minus date of first dose in EP0085 plus one in days. If the last dose date on the Study Termination / Early Discontinuation page is missing the last dose date will be captured from the Drug Dosing Log CRF. Gaps in BRV treatment or days on the Drug Dosing Log CRF with unknown dosing and/or partial missing exposure date will not be subtracted from the total duration of exposure.

Total study medication duration in subject-years will be calculated as the total duration of exposure in days divided by 365.25.

The duration of exposure to study medication will be summarized by study group for all subjects in the SS and will be presented in a table by summary statistics.

The subject cumulative exposure duration will then be classified into one of the following categories: >0 month, ≥3 months, ≥6 months, ≥12 month, ≥18 month, ≥24 months, ≥ 36 months, ≥ 48 months, and so forth in 12-month increments up to the maximum duration of

exposure and will be presented as the number and percentage of subjects in each duration category by BRV overall and by modal dose group. Percentages for BRV overall will be computed based on the Safety Set. Percentages for the modal dose group will be computed based on the number of subjects exposed overall or within each duration of exposure.

9.1.2 Study medication dose

The total cumulative dose will be defined as the sum of the doses across all study days. The mean daily dose is defined as cumulative dose divided by total days on study medication.

The modal daily dose will be calculated across all study days on or after the day of first dose of BRV and up to and including the day of last dose of BRV. Modal daily dose is the most frequently taken daily dose during the study. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as follows:

Category	Definition
5 mg/day	<20mg/day
20mg/day	≥20mg/day to <50mg/day
50mg/day	≥50mg/day to <100mg/day
100mg/day	≥100mg/day to <150mg/day
150mg/day	≥150mg/day to <200mg/day
200mg/day	≥200mg/day

The mean daily dose, modal daily dose, and modal daily dose category will be summarized using descriptive summary statistics by study group.

A summary of each subject's exposure will be presented in a listing.

9.2 Primary safety variables

9.2.1 Definition of treatment-emergent adverse events

AEs will be classified as either pre-treatment or treatment-emergent. Pre-treatment AEs are defined as AEs which had onset prior to the date of the first dose of BRV in EP0085 study. Treatment-emergent AEs (TEAEs) are defined as AEs that had onset on or after the day of first BRV dose in EP0085 study. 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 the month and year of the first BRV dose or the year of onset (when only year is specified) is the same as the year of first BRV dose.

9.2.2 Summaries of TEAEs

Pre-treatment AEs will be provided in a subject data listing; no summary of pre-treatment AEs are planned. Summaries will be for TEAEs and will be provided overall by combining Evaluation Period, Down-Titration Period, and Study Drug-Free Period unless otherwise indicated.

The following summary of TEAEs will be provided:

- Incidence of TEAEs – overview (overall and by study periods)

The following summaries of TEAEs will be provided by MedDRA SOC and PT:

- Incidence of TEAE (overall and by study periods)
- Incidence of TEAEs by safety time interval (overall)
- Incidence of TEAEs above reporting threshold of 5% of subjects (overall)
- Incidence of non-serious TEAEs above reporting threshold of 5% of subjects (overall)
- Incidence of TEAEs by maximum intensity (overall and by study periods)
- Incidence of TEAEs by relationship (overall and by study periods)
- Incidence of TEAEs leading to permanent discontinuation of study drug (overall)
- Incidence of treatment-emergent SAE (overall and by study periods)
- Incidence of treatment-emergent SAE by relationship (overall)
- Incidence of fatal TEAEs by relationship (overall)
- Incidence of TEAEs of special interest (overall and by study periods)
- Incidence of TEAEs requiring dose change (overall and by study periods)
- Incidence of TEAEs related to COVID-19 vaccination (overall and by study periods)

For by-study period summary tables, TEAEs will be attributed according to the onset date.

Three-month safety time interval will be used to summarize data up to and including the maximum duration of exposure to BRV. TEAEs which had onset prior to or on the date of the last dose of BRV are included in summaries by 3-month time intervals. A subject is included in a 3-month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval according to the onset date as the nominator.

9.2.2.1 Incidence of treatment-emergent adverse events

TEAEs will be presented by SOC and PT. The incidence of TEAE table will include the number and percentage of subjects and number of events by SOC and PT. For the number of subjects by SOC/PT, if a subject experiences the same SOC/PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects in the SS. The number of events at each level of SOC and PT will also be summarized.

The summary of AEs will be presented in alphabetical order by SOC. Within each SOC, PTs will be sorted by descending order of total frequency (ie, frequency across all study groups). If the total frequency for any two or more PTs is equal within a SOC, the PTs will be presented in alphabetical order.

All TEAEs will be presented in a listing with a glossary.

9.2.2.2 Withdrawal due to adverse events

All TEAEs collected with a study drug action taken as "Drug permanently withdrawn" will be summarized in a table by SOC and PT in a manner similar to that described in the Section 9.2.2.1. All AE leading to study discontinuation or permanently withdrawal of study drug will be listed by subject.

9.2.2.3 Serious adverse events

Serious TEAEs will be presented in a table by SOC and PT in a manner similar to that described in the Section 9.2.2.1. All SAE will be listed by subject.

9.2.2.4 Adverse events of special interest

The following AEs are considered as AEs of special interest:

- autoimmune nephritis
- nephritis
- nephritis allergic
- tubulointerstitial nephritis
- uveitis syndrome
- Potential Hy's Law

The TEAE of special interest, which will be captured on the CRF page, will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

9.2.2.5 Relationship of adverse events to study drug

The relationships of TEAE will be either "Related" or "Not Related" according to the CRF entry. AEs with missing relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship.

The AE data will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

9.2.2.6 Intensity of adverse event

Summary of TEAEs will be presented by maximum intensity:

In the TEAE by maximum intensity table, if a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted only once according to the maximum intensity within that SOC or PT (severe > moderate > mild).

AEs with missing intensity will be presented on tables as "Severe" but will be presented in the data listing with a missing intensity.

The AE data will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

9.2.2.7 Adverse event requiring dose change

All TEAEs collected with a study drug action taken as “Dose reduced”, "Dose increased" or "Drug temporary interrupted" will be summarized in a table by SOC and PT.

9.2.2.8 Adverse events related to COVID-19 vaccination

The TEAE related to COVID-19 vaccination, which will be captured on the CRF page, will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

9.3 Other safety variables

Unless otherwise indicated baseline is defined as the last non-missing data collected prior to the first dose of study medication (including Placebo and BRV) in core study. Core study is defined as the first study a study participant was enrolled in.

9.3.1 Laboratory measurements

9.3.1.1 Hematology, biochemistry and urinalysis parameters

All summaries will be based on the standard international units.

The observed values and change from baseline will be presented descriptively for hematology and biochemistry assessments with numeric values by study group for each scheduled visit (not including EV) and for Last Value. Change from baseline will be presented for each scheduled post-baseline visit and Last Value. Last Value is the last available assessment during treatment with BRV.

For the qualitative urinalysis parameters, the number and percentage of subjects with each response category will be summarized for Baseline, scheduled visits and Last Value.

Possibly clinically significant treatment-emergent (PCST) abnormalities for laboratory values will be summarized by visit and at Last Value as stated above. The PCST abnormality will also summarized with shift tables of post-baseline results versus baseline results. Details of PCST criteria are available in Section 12.1.

Urine pregnancy test results will not be summarized but will be provided in a subject data listing.

9.3.1.2 PDILI laboratory measurements

The number and percentage of subjects with PDILI will be summarized in table by study group. In addition, the number and percentage of subjects meeting ALT or AST or both, total bilirubin and symptoms criteria will be summarized in table.

Listings of subjects with PDILI include alcohol use within past 6 months, the laboratory results for ALT, AST and Total bilirubin, symptoms of hepatitis or hypersensitivity, action and follow up will be provided only if any subject reporting PDILI.

9.3.2 Vital signs

The observed value and change from baseline for vital signs parameters will be presented at each scheduled visit and Last Value by study group.

The number and percentage of subjects with any PCST values, any PCST low values, and any PCST high value will be summarized. Percentages will be relative to the number of subjects with an assessment within each visit. Details of PCST criteria are available in Section 12.1.2.

9.3.3 Body weight

Same analyses stated for vital signs will be applied. The results will be reported as an item of vital signs.

9.3.4 Electrocardiograms (ECG)

As for the reported ECG parameters, the observed values and change from baseline will be presented descriptively by study group for each scheduled visit and for Last Value.

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 Baseline, each visit during the Evaluation Period for which an ECG is scheduled to be performed, and Last Value. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Same summary will be provided to ECG classification of QTc.

A listing of subjects will be provided, in which details of abnormality and ECG reader (investigator or cardiologist) will be included. Subjects with QTc results >= 500 msec or QTc change from Baseline >= 60 msec will be flagged.

9.3.5 Physical examination

A standard physical examination will be performed at time points specified in the protocol. No summaries of physical examination are planned because physical examination findings were not recorded on the CRF, and clinically significant new or worsened abnormalities will have to be reported as AEs.

9.3.6 Neurological examination

A listing of abnormal neurological examination findings or examination that was not done will be provided; no summaries of neurological examination findings are planned because clinically significant new or worsened abnormalities will have to be reported as AEs.

9.3.7 Columbia-suicide severity rating scale

Suicidality will be assessed by trained study personnel using the Columbia-Suicide Severity Rating Scale (C-SSRS). This scale will be used for Baseline/Selection as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed at time points specified in the schedule of study assessments. Because clinical events of interest will be recorded as AEs or serious AEs, no study variable is defined for this assessment and no summary 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.

10 PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable for this study.

11 REFERENCES

Not applicable

12 APPENDICES

12.1 PCST criteria

12.1.1 Laboratory assessments - PCST

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

12.1.1.1 Hematology

Table 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

PARAMETER	AGE RANGE	UNIT (standard)	ABNORMALITY CRITERIA (standard)
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; PCST=possibly clinically significant treatment-emergent; y= year. A month is defined as 30 days; a year is defined as 365.25 days.

12.1.1.2 Blood chemistry

Table 3: Chemistry PCST criteria

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

PARAMETER	AGE RANGE	UNIT (standard)	ABNORMALITY CRITERIA (standard)
	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; Cr CL=creatinine clearance; 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; PCST=possibly clinically significant treatment-emergent; 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

12.1.1.3 Urinalysis

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

Table 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)

PARAMETER	Original Scale	4-point Scale for PCST
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

12.1.2 Vital sign assessments – abnormal

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

Table 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
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

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
	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(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

13.1 Amendment 1

Rationale for the amendment

The main purpose of this amendment is to align the SAP with Protocol Amendment 3 and Protocol Amendment 3.1 (Japan).

Modifications and changes

Global changes

In Japan, a cohort of direct enrollers was added.

Specific changes

Change #1

Study title

AN OPEN-LABEL, MULTICENTER, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN JAPANESE SUBJECTS ≥16 YEARS OF AGE WITH PARTIAL SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

Has been changed to:

AN OPEN-LABEL, MULTICENTER, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN ~~**JAPANESE**~~ SUBJECTS ≥16 YEARS OF AGE WITH PARTIAL SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

Change #2

1 INTRODUCTION (last sentence)

… The SAP is based on the following study document: Final Protocol Amendment 1 26 July 2017 and CRF version 2.0.

Has been changed to:

… The SAP is based on the following study document: Protocol Amendment 3 and Protocol Amendment 3.1 (Japan) and Case Report Form (CRF) version 8.0.

Change #3

2.2.1 Safety variables

2.2.1.1 Primary Safety variables

The primary safety variables include:

- AEs

- Withdrawal due to AEs
- Occurrence of SAEs

2.2.1.2 Secondary Safety variables

The secondary safety variables include:

- Laboratory tests (blood chemistry, hematology, and urinalysis)

…

Has been changed to:

2.2.1.1 Primary Safety variables

The primary safety variable is AEs.

2.2.1.2 Other safety variables

The other safety variables are as follows:

- Laboratory tests (blood chemistry, hematology, and urinalysis)

…

Change #4

2.2.2 Efficacy variables

The efficacy variables include:

- Percent reduction in partial seizure frequency per 28 days from Baseline of EP0083 or N01358 to the Evaluation Period
- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥ 50% reduction in seizure frequency from the Baseline Period of EP0083 or N01358
- Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.
- Percentage of subjects continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

Has been changed to:

2.2.2 Efficacy variables

The efficacy variables for rollover subjects in China and Japan include:

- Percent reduction in partial seizure frequency per 28 days from Baseline of EP0083 or N01358 to the Evaluation Period

- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥ 50% reduction in partial seizure frequency from the Baseline Period of EP0083 or N01358

Efficacy variables for direct enrollers in Japan include:

- Percent reduction in partial seizure frequency per 28 days from 8 weeks prior to BRV administration to the Evaluation Period
- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in partial seizure frequency from 8 weeks prior to BRV administration

Efficacy variables for all subjects (rollovers in China and Japan and direct enrollers in Japan):

- Percentage of subjects continuously seizure-free for partial seizure for at least 6 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for partial seizure for at least 12 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for all seizure types (partial, generalized and unclassified epileptic seizure) for at least 6 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for all seizure types (partial, generalized and unclassified epileptic seizure) for at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

Change #5

2.3 Study design and conduct

EP0085 is a Phase 3, open-label, LTFU, multicentre, noncomparative, and dose flexible study. The subject population will be Japanese subjects (≥16 years of age) with partial seizures with or without secondary generalization. Subjects must complete the Treatment and Transition Period of EP0083 prior to enrolment into EP0085. In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment. Subjects from N01379 can enter EP0085 at a dose up to 200mg/day. After Visit 1, the next visit for subjects entering from N01379 will be Visit 4 (Visit 2 and Visit 3 will not be conducted). Subsequent visits will be conducted according to the visit schedule provided in protocol Section 5.3, Table 5–2 (final version, 22 Nov 2016). The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study

and must always be administered as a symmetrical morning and evening dose except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study drug in the last week of down-titration is given only in the morning.

The study duration per subject is based on the definition of the following periods:

- Evaluation Period (Visit 1 to End of Study Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in EP0083 and N01379 will enter the Evaluation Period

- Down-Titration Period (up to 4 weeks): If the subject is discontinuing study drug, the Investigator will first plan an EDV followed by the progressive down-titration of study drug. During the Down-Titration 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 for 1 week should be included prior to the 2-week Study drug-Free Period.

- 2-week Study Drug-Free Period: After completion of the Down-Titration Period, or for those subjects who for extenuating circumstances do not complete a Down-Titration Period, the subject will be required to enter a 2-week Study drug-Free Period, followed by a Final Visit (FV).

Has been changed to:

2.3 Study design and conduct

EP0085 is a Phase 3, open-label, long-term follow-up (LTFU), multicenter, noncomparative, and dose flexible study being conducted in Japan and China. The population are subjects (≥16 years of age) with partial seizures with or without secondary generalization. Subjects of a minor age are included only where legally permitted and ethically accepted. In Japan, subjects meeting the inclusion and exclusion criteria as specified in the study protocol can be directly enrolled. Rollover subjects must complete the Treatment and Transition Period of EP0083 prior to enrolment into EP0085. In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Directly enrolled subjects in Japan will have their eligibility confirmed at the Screening Visit (SV). SV occurs -2 to -21 days before BRV administration. Directly enrolled subjects in Japan and rollover subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment.

Subjects from N01379 can enter EP0085 at a dose up to 200mg/day. After Visit 1, the next visit for subjects entering from N01379 will be Visit 4 (Visit 2 and Visit 3 will not be conducted). Subsequent visits will be conducted according to the visit schedule according to EP0085 study protocol. (see Table 1). The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered as a symmetrical morning and evening dose except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study drug in the last week of down-titration is given only in the morning.

The study duration per subject is defined as follows:

• Screening Visit (Visit 0, up to 3 weeks before the Entry Visit (EV) for direct enrollers in Japan only)

• Evaluation Period (Visit 1 to End of Study Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in EP0083 and N01379 will enter the Evaluation Period

• Down-Titration Period (up to 4 weeks):

- If the subject is discontinuing study drug, the Investigator will first plan an EDV followed by the progressive down-titration of study drug.

- During the Down-Titration 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 for 1 week should be included prior to the 2-week Study Drug-Free Period.

• 2-week Study Drug-Free Period: After completion of the Down-Titration Period, or for those subjects who for extenuating circumstances do not complete a Down-Titration Period, the subject will be required to enter a 2-week Study Drug-Free Period, followed by a Final Visit (FV).

Visits should occur on the specified Visit/Week. A ±7 day 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.

EP0085 will continue until the market approval of BRV or one year after each subject has entered into EP0085, or until the sponsor decides to close the study, whichever comes first. In the event that market approval is not obtained in the participant country, the subject will be able to continue in EP0085 for two years after entering EP0085.

In Japan and China, EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

At selected sites in Japan, Japanese subjects may participate in an additional study (EP0118) with the intravenous formulation of BRV without withdrawing from EP0085. Ten evaluable subjects are planned for EP0118, and the total duration in the study for each subject is 7 days. The study period of EP0118 will be included in that of EP0085. Subjects will continue to receive their current dose of BRV at the time of entry that will remain stable for the duration of EP0118. Subjects who complete or withdraw from EP0118 will be given the opportunity to resume their participation in EP0085 with oral BRV treatment. In the event that a subject withdraws from EP0118 and is required to taper off BRV, the subject will return to EP0085 and taper using BRV tablets. Adverse events and concomitant treatment(s)/medication(s) that occur or are administered during EP0118 will be recorded in EP0118. Ongoing AEs and concomitant medication(s)/medical procedure(s) originating from the EP0118 will be recorded and followed in EP0085 until resolution or until the status of AE and/or concomitant medications are stable. All other data reported for EP0118 will be captured in the EP0118 database. Per the EP0118 protocol, the study (EP0118) will require hospitalization. Hospitalization for study participation does not need to be reported as an SAE.

Change #6

2.4 Determination of sample size

For this open-label LTFU study, no sample size calculation was performed. The sample size will depend upon recruitment into and completion of the previous studies. It is estimated that approximately 124 subjects will enter the study based on the assumption that at least 90% of randomized subjects will complete EP0083 or enter from N01379 sites in Japan.

Has been changed to:

2.4 Determination of sample size

For this open-label LTFU study, no sample size calculation was performed. The sample size will depend upon recruitment into and completion of the previous studies. Overall, approximately 217 subjects are planned for enrollment. In Japan, it is estimated that approximately 127 subjects will enter the study. This estimate assumes that at least 90% of randomized Japanese subjects will complete EP0083 (approximately 90 subjects) or enroll from N01379 sites in Japan (7 subjects) and that 30 Japanese subjects will be directly enrolled in this study. Likewise, this estimate assumes that at least 90% of randomized Chinese subjects will complete EP0083 (approximately 90 subjects).

Change #7

3 DATA ANALYSIS CONSIDERATIONS

The statistical analysis details are addressed in following sections. Subjects from N01379 and from EP0083 will be analysed separately as well as pooled as an overall study population, no comparison will be performed.

Has been changed to:

3 DATA ANALYSIS CONSIDERATIONS

~~The statistical analysis details are addressed in following sections. Subjects from N01379 and from EP0083 will be analysed separately as well as pooled as an overall study population, no comparison will be performed.~~

Change #8

3.1 General presentation of summaries and analyses

…

For continuous parameters, descriptive statistics will include number of subjects with available measurements (n), mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum, and maximum. Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer.

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

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

Summaries for the subject disposition, demographics, baseline characteristics, medical history, protocol deviation, prior and concomitant medications and study drug exposure will present results for study groups described in the later Section 3.2.2, respectively. All the safety variables and efficacy variables will present results for study groups, respectively.

Statistical outliers are defined as values that are discordant with other values and are clinically implausible. Any outliers will be reviewed during the data evaluation meeting (DEM) prior to database lock or in an interim report.

Subject data listings will be provided and will present source data and key derived variables for statistical analyses.

Has been changed to:

3.1 General presentation of summaries and analyses

…

For continuous parameters, descriptive statistics will include number of subjects with available measurements (n), mean, standard deviation (SD), median, ~~25th percentile, 75th percentile~~, minimum, and maximum. Decimal places for descriptive statistics will always apply the following rules:

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

<u>All summaries will be descriptive; no statistical hypothesis testing is planned.</u>

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

~~Summaries for the subject disposition, demographics, baseline characteristics, medical history, protocol deviation, prior and concomitant medications and study drug exposure will present results for study groups described in the later Section 3.2.2, respectively. All the safety variables and efficacy variables will present results for study groups, respectively.~~

~~Statistical outliers are defined as values that are discordant with other values and are clinically implausible. Any outliers will be reviewed during the data evaluation meeting (DEM) prior to database lock or in an interim report.~~

~~Subject data listings will be provided and will present source data and key derived variables for statistical analyses.~~

Change #9

3.2.1 Analysis time points

3.2.1.1 Relative day

Relative day will be calculated as the current date minus the date of first dose of study drug plus 1 for days on treatment. The day prior to first dose will be Day -1, the day of first dose in this study will be Day 1. The days during BRV treatment will be Day plus a positive integer (eg, Day 2, 28).

For days after the last dose of study drug (in Down-Titration Period and 2-week Study Drug-Free Period), the relative day will be calculated as the current date minus the date of last dose of study drug including a "+" to denote post treatment days (eg, the day after the last dose will be Day +1).

Relative day will not be calculated for partial dates.

Has been changed to:

3.2 Analysis time points

3.2.1 First and last dose of BRV

Unless otherwise noted, all references to the first dose of BRV in this SAP refer to the first dose of BRV during EP0085 (ie, not the first dose of BRV from the previous study in which subjects participated in prior to EP0085). Unless otherwise noted, all references to the last known dose of BRV in this SAP refer to the last dose of BRV taken across any study periods (ie, the last dose of BRV across both the Evaluation and Down-Titration Periods).

3.2.2 Relative day

Relative day will be calculated as follows:

- For days prior to the first dose of BRV, the relative day is the current date minus the date of first dose of BRV. The relative day prior to first dose will be Day -1.

- For days on or after the first dose of BRV and on or prior to the last dose of BRV, the relative day is the current date minus the date of first dose of BRV plus 1. The relative day of first dose will be Day 1.

- For days after the last dose of BRV, the relative day is the current date minus the date of last dose of BRV. The relative day 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 or missing dates.

Change #10

A new section has been added:

3.2.3 Screening Visit

The SV only applies to direct enrollers in Japan and will be performed between Day -21 and Day -2 prior to Visit 1 (EV). The following assessments will be performed at SV:

Study	Visit	Assessments
EP0085 direct enrollers in Japan	Visit 0	Demography, medical history, epilepsy history AED history, vital signs, body weight, physical examination, neurological examination, 12-lead ECG, laboratory safety assessments, seizure counts, ongoing AE reporting (see more information in Section 9.2), C-SSRS, medical procedures, ongoing concomitant medications (including AEDs and non-AEDS).

Change #11

3.2.2 Study periods

The following study periods are defined for the classification in summary that are based on the study design:

Evaluation Period	The Evaluation Period starts on the date of Visit 1 and ends on the date of End of Study Visit for subjects who completed study or were converted to commercial BRV or on the date of EDV for discontinued subjects.
Treatment Period	This period comprises the duration from the day of the first dose to the day of last the last dose throughout the Evaluation Period and the Down-Titration Period.
Down-Titration Period (up to 4 weeks)	The Down-Titration Period starts with the first dose date of decreasing dose to the last day within the 4 weeks, or the date of discontinuation during the Down-Titration Period.
Study Drug-Free Period (2 weeks)	The 2-week Study Drug-Free Period starts with the first day after the last dose of Down-Titration Period up to two week later or the last following up date.

Has been changed to:

3.2.5 Study periods

The following study periods are defined for the classification in summary that are based on the study design:

Baseline Period	For rollover subjects from EP0083, the Baseline Period is defined as study days on or after EP0083 Visit 1 date and prior to EP0083 Visit 3 date. For rollover subjects from N01379, the Baseline Period is defined as study days on or after N01358 Visit 1 date and prior to N01358 Visit 3 date. For direct enrollers, the Baseline Period is defined as study days on or after EP0085 Visit 0 date and prior to EP0085 Visit 1 date.
Evaluation Period	The Evaluation Period starts on the date of Visit 1 and the following algorithm is used to determine the end date: If the subjects enter the Down-Titration Period: - for completed subjects, which is indicated by the CRF "Study Termination" form (Complete subject), the Evaluation Period ends on the date of End of Study Visit date. - for discontinued subjects, which is indicated by the CRF "Study Termination" form (Dropout), the Evaluation Period ends on the date of EDV date. If the subjects do not enter the Down-Titration Period: For complete / discontinued subjects who do not enter the Down-Titration Period, the end of Evaluation Period will be the date of last dose of BRV.
Down-Titration Period (up to 4 weeks)	If the subject is discontinuing BRV, the Investigator will first plan an EDV followed by the progressive down-titration of study drug. A subject is considered entering Down-Titration Period only if the subject has an EDV and has at least 1 dose of study drug after the date of EDV, the start date of Down-Titration Period is set as 1 day after the date of EDV, and the Down-Titration Period ends on date of last dose of BRV. A subject without an EDV but having a termination CRF or with an EDV but without any dosing of study drug after the EDV will not have the Down-Titration Period, and no artificial Down-Titration Period will be created for analysis.
Study Drug-Free Period (2 weeks)	After completion of the Down-Titration Period, or for those subjects who for extenuating circumstances do not

complete a Down-Titration Period, the subject will enter a 2-week Study Drug-Free Period, followed by a Final Visit.

A subject is considered entering the Study Drug-Free Period if the subject has at least 1 contact (scheduled visit, unscheduled visit, or telephone contact) after the date of last dose of BRV. The 2-week Study Drug-Free Period starts 1 day after the date of last dose of BRV and ends on the date of Final Visit.

For complete / discontinued subjects who do not enter the Down-Titration Period, the Study Drug-Free Period starts 1 day after the last dose of BRV and ends on the date of Final Visit.

Change #12

3.2.3 Study groups

Subjects from N01379 and EP0083 need to be analyzed separately. For EP0083 a detailed segmentation by dose group is necessary. All relevant Tables, Figures and Listings will present the group titles as:

- EP0083 Placebo
- EP0083 BRV 50mg/day
- EP0083 BRV 200mg/day
- EP0083 BRV all
- EP0083 Total
- N01379
- All Subjects

Unless otherwise specified, results will be presented for each grouping described above.

Has been moved to:

3.6 Treatment assignment and study groups

It is expected that subjects will receive treatment as assigned in accordance with the study design.

Rollover subjects from N01379, EP0083, and directly enrolled subjects need to be analyzed separately. For EP0083 a detailed segmentation by drug group is necessary. Unless otherwise specified, results will be presented for each grouping described below:

For tables and figures the study groups will be presented as follows:

- EP0083 Placebo
- EP0083 BRV All

- EP0083 Total
- N01379
- Direct Enrollers
- All Subjects

For subject listings, the study group will be presented as follows:

- EP0083 Placebo
- EP0083 BRV 50mg/day
- EP0083 BRV 200mg/day
- N01379
- Direct Enrollers

For submission purpose, the subgroup tables and figures will be presented by Japan and China. In Japan subgroup tables and figures, the study groups will be presented in the same manner as overall. In China subgroup tables and figure, given that only the EP0083 rollover subjects will be enrolled from China, the study group will be presented as follows:

- EP0083 Placebo
- EP0083 BRV All
- All Subjects

Change #13

A new section 3.2.6 Monthly time intervals has been added:

3.2.6 Monthly time intervals

In terms of the analysis, a month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days). The following definitions of 3-month and 6-month intervals are based on 30-day months where the date of first dose of BRV is Day 1:

Interval	Duration Definition
Month 1-3	Day 1-90
Month 4-6	Day 90-180
Month 7-9	Day 181-270
Month 10-12	Day 271-360
Month 13-15	Day 361-450
Month 16-18	Day 451-540
Month 19-21	Day 541-630
Month 22-24	Day 631-720
Month 1-6	Day 1-180
Month 7-12	Day 181-360

Month 13-18	Day 361-540
Month 19-24	Day 541-720

Change #14

3.2.4 Mapping of assessments performed at Early Discontinuation Visit

Efficacy and safety assessments at an Early Discontinuation Visit (EDV) that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. Such assessments will also be considered for Last Value.

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

The results of unscheduled visit will only be presented in subject listing for safety and efficacy variables.

Has been changed to:

~~3.2.4 Mapping of assessments performed at Early Discontinuation Visit~~

~~Efficacy and safety assessments at an Early Discontinuation Visit (EDV) that correspond to a scheduled visit will be summarized at the scheduled visit corresponding to the EDV if the assessment was scheduled to occur at that visit. Such assessments will also be considered for Last Value.~~

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

~~The results of unscheduled visit will only be presented in subject listing for safety and efficacy variables.~~

A new section 3.2.7 is added:

3.2.7 Last Value on BRV Treatment

Last Value for clinical laboratory parameters, vital signs, and ECGs is the last available result obtained after the first dose of BRV and prior to or on the date of last dose of BRV. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each laboratory parameter.

Change #15

3.3 Definition of Baseline values

The baseline value for all safety and efficacy variables is defined as the last non-missing data collected prior to the first dose of study medication in study EP0083 or N01358, unless addressed otherwise for a specific type of data.

Has been changed to:

3.3 Definition of Baseline values

For rollover subjects, the baseline value for all safety and efficacy variables is defined as the last non-missing data collected prior to the first dose of study medication in study EP0083 or N01358, unless addressed otherwise for a specific type of data.

For direct enrollers in Japan, the baseline value is defined as the last non-missing data collected prior to the first dose of study medication in study EP0085, unless addressed otherwise. For seizure frequency, the baseline is defined as the seizure counts collected from 8 weeks prior to the first BRV administration. This baseline seizure frequency for direct enrollers is consisted of subject's own document (eg, DRC) and the data in DRC for EP0085 between SV and EV.

Change #16

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the evaluation of safety and efficacy outcome. Protocol deviations will be identified during ongoing data monitoring process. All potential protocol deviation will be reviewed at the DEM. In the DEM the important protocol deviation will be identified on a subject level.

Has been changed to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the evaluation of safety and efficacy outcome. Protocol deviations will be identified during ongoing data monitoring and cleaning process and ~~All potential protocol deviation~~ will be reviewed in the Data Cleaning Meetings . The impact of the protocol deviations to the analysis will be discussed in Data Evaluation Meeting.

Change #17

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of subjects who signed an informed consent form, enrolling from either study EP0083 or from study N01379. Subject disposition will be based on ES for presentation. This analysis set is referred to as “All Subjects Screened”.

Has been changed to:

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of subjects who signed an informed consent form in EP0085, enrolling from study EP0083 or from study N01379 or are directly enrolled into EP0085 in Japan. This analysis set is also referred to as “All Subjects Screened”.

Change #18

3.8 Changes to protocol-defined analyses

No applicable.

Has been changed to:

3.8 Changes to protocol-defined analyses

According to the Protocol Amendment 3 and Protocol Amendment 3.1 (Japan), the mental and psychiatric status are included as the other safety variables. However, both variables are not collected in EP0085 CRF and will be removed in the future protocol amendment. The relevant analysis will not be conducted.

Change #19

The following new paragraphs are added to section 4.1 Handling of missing data:

Subjects participating in EP0118 while also enrolled in EP0085 will have missing data for seizure frequency and drug dosing while participating in the EP0118 trial. As the duration of the EP0118 study will be short (3-7 days), no imputation for data missing due to participation in EP0118 will be performed. Subjects will be assigned the same dose in EP0118 as that assigned in EP0085 for the two weeks prior to the start of EP0118. As such, time during the EP0118 study will not be subtracted from the exposure calculations (eg, exposure will be from the start of BRV treatment in the EP0085 study until the date of last dose of BRV in EP0085).
For the calculation of variables related to seizure frequency, the dates during participation in EP0118 will be considered as not done for the purpose of efficacy analyses for trial EP0085 (eg, these dates will not be considered as days evaluated for seizure frequency). Due to the short nature of the EP0118 study, only a few days of seizure frequency data are expected to be missing due to participation in EP0118 unless otherwise specified (eg, for the evaluation of seizure freedom).

Change #20

4.3 Multicenter studies

The disposition of subject by study center will present in the summary table by study center. The information of study centers will also be identified in the Subject Disposition listing.

Has been changed to:

4.3 Multicenter studies

The disposition of subject by study center will present in the summary table by study center. The information of study centers will also be identified in the Subject Disposition listing. Efficacy and safety outcomes will not be assessed for individual study center due to the low expected number for enrollment within each study center.

Change #21

A new section regarding COVID-19 has been added:

A new Coronavirus Disease 2019 (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 9.2.2.9) to describe the impact on the interpretability of efficacy and safety endpoint due to COVID-19 will be performed. AE related to COVID-19 vaccination will be flagged in the AE listings.

Change #22

6.1 Demographics

The age, weight and height as continuous variables, the age classifications and the sex as categorical variables will be summarized by study group.

The age of subject will be derived as following:

Age[years] =INT [(The date of signed informed consent - The date of birth)/365.25]

The result from above derivation will be kept as integer and the unit of age is years.

The demographic variables will be listed by subject.

Has been changed to:

6.1 Demographics

Age, age category, gender, racial group, ethnicity, ethnicity subgroup (Japan or China), body weight (kg), height (cm), body mass index (BMI) (kg/m2), and BMI category will be summarized by study group for the Safety Analysis Set.

The age will be categorized according to the following categories:

- 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
- clinicaltrials.gov: ≤18, 19 to <65 and ≥65 years

The BMI will be categorized according to the following category:

- <18.5, 18.5 to <25, 25 to <30, 30 to <40, ≥40

Age will be calculated based on the date of informed consent and date of birth. The result will be kept as integer and the unit of age is years.

A birth date of each subject provided from the feeder studies is imputed to be born on the first day of that month (yyyy-mm-01).

The demographic variables will be listed by subject.

Change #23

6.2 Other Baseline characteristics

The following epilepsy-related background variables will be summarized by study group:

- Vagal nerve stimulation
- Etiology of epilepsy
- Epileptic seizure profile
- Classification of epileptic syndrome
- Focus localization
- History of epileptic seizures
- Seizure types during Baseline
- Baseline partial seizure frequency

The number and percentage of subject who had vagal nerve stimulation (VNS) at baseline will be summarized in a table.

All above-mentioned baseline characteristics of study EP0083 and N01358 will be listed by subject.

In addition, childbearing potential and lifestyle-related variables for PDILI (potential drug-induced liver injury) assessment will be listed by subject.

Has been changed to:

6.2 History of epilepsy

The following epilepsy-related background variables will be summarized by study group:

- Vagus nerve stimulation (VNS) at Screening/Baseline
- History of epileptic seizures
- Classification of epileptic syndrome
- Baseline seizure type and partial seizure frequency

For all subjects, the VNS information will be obtained from EP0085 CRF form: Vagus Nerve Stimulation Status at Screening/Baseline. The number and percentage of subject who had VNS at study entry will be summarized in a table. A listing of VNS status at study entry and VNS setting at the subsequent visits will be provided.

For rollover subjects, the history of epileptic seizures, classification of epileptic syndrome, seizure types during Baseline, and Baseline partial seizure frequency, the data will be

obtained from the EP0083 study and N01358 study (for subjects from N01379). For direct enrollers, the data will be obtained from EP0085 CRF forms.

All above-mentioned baseline characteristics will be listed by subject.

Change #24

6.3 Medical history and concomitant diseases

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 by study group by the primary system organ class (SOC) and preferred term (PT) according with MedDRA version 18.1. Additionally, the number and percentage of subjects with concomitant diseases and conditions will be summarized by SOC and PT.

A listing of subjects with concomitant medical procedures will be provided.

Has been changed to:

6.3 Medical history conditions and procedure history

For rollover subjects, the medical history conditions and procedure history will be obtained directly from the Medical History CRFs and the Procedure History CRFs of the EP0083 and N01358 (for rollover subjects from N01379). If there is any new medical history condition, it will be collected in the Medical History Update form in EP0085. For direct enrollers, the medical history conditions and procedure history will be obtained from the Medical History CRFs and the Procedure History CRFs of EP0085. Reported medical history conditions are coded according with MedDRA version 18.1 Medical procedures are not coded. Start and stop date are documented partially with month and year only (yyyy-mm). No date imputation is foreseen.

6.3.1 Previous and ongoing medical history conditions

The number and percentage of subjects with a medical history condition, including both resolved and ongoing conditions, will be summarized by study group by the primary System Organ Class (SOC) and Preferred Term (PT).

A listing of subjects with previous and ongoing medical history conditions will be provided.

6.3.2 Procedure history and concomitant procedures

A listing of subjects with procedure history and concomitant procedures will be provided.

Change #25

6.3 Medical history and concomitant diseases

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 by study group by the primary system organ class (SOC) and preferred term (PT) according with

MedDRA version 18.1. Additionally, the number and percentage of subjects with concomitant diseases and conditions will be summarized by SOC and PT.

A listing of subjects with concomitant medical procedures will be provided.

6.4 Prior and concomitant medications

All prior and concomitant medications will be coded according to the WHODD version September 2015. A prior medication is defined as any medication with a stop date prior to the first dose of study drug. A concomitant medication is defined as any ongoing medication or with a stop date on or after the first dose of study drug.

If necessary, the same imputation rules for incomplete dates as for AEs will be applied. Please refer to Section 9.1.1.

The number and percentage of subjects taking prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term by study group using the SS as follows;

- History of antiepileptic drugs (AEDs) use prior to entry into the feeder study (EP0083 or N01358)
- Number of previous AEDs at the feeder study (EP0083 or N01358) entry
- AEDs taken at study entry
- Concomitant AEDs
- Non-AEDs taken at study entry

Has been changed to:

6.4 Prior and concomitant medications

All prior and concomitant medications will be coded according to the WHODD version September 2017. The AED is defined according to the list of antiepileptic drug as indicated in Appendix 3 of the study protocol.

6.4.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AEDs at study entry will be summarized for Safety Set by primary therapeutic group (Anatomic Therapeutic Class [ATC] level 1), therapeutic subgroup (ATC level 2), and preferred drug name for the Safety Analysis Set.

For rollover subjects the medications will be the non-AEDs taken at study entry of the previous feeder study and the information will be obtained from CRF form “Prior and Concomitant Medications (including AEDs)” from EP0083 and CRF form “Prior and Concomitant Medications ” from N01358 (for subjects from N01379). For direct enrollers the medication will be the non-AEDs taken at study entry of EP0085 and the information will be obtained from EP0085 CRF form “Concomitant Medications (including AEDs)”.

6.4.2 History of previous AED use

The number and percentage of subjects who had taken at least 1 previous AED will be summarized overall and by preferred drug name for the Safety Set. For rollover subjects the previous AEDs are AEDs taken and discontinued prior to entry into the previous feeder study and the information will be obtained from CRF form "History of Previous Antiepileptic Drug Treatment" from EP0083 and N01358 (for subjects from N01379). For direct enrollers the previous AEDs are AEDs taken and discontinued prior to EP0085 and the information will be obtained from EP0085 CRF form "History of Previous Antiepileptic Drug Treatment".

6.4.3 Number of previous AEDs

The number and percentage of previous AEDs will be summarized based on the following categorization: 0-1 AEDs, 2-4 AEDs, and ≥5 AEDs. The definition of previous AED use will be the same as section 6.4.2.

6.4.4 AEDs taken at study entry

The number and percentage of subjects taking AEDs at study entry visit will be summarized by preferred drug name for the Safety Set. For rollover subjects the medications will be the AEDs taken at study entry of the previous feeder study and the information will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications(AEDs only)" from N01358 (for subjects from N01379). For direct enrollers the medication will be the AEDs taken at study entry of EP0085 and the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

6.4.5 Concomitant AEDs

A concomitant AED is an AED which was taken during administration of BRV in EP0085 study, regardless of the start and stop date of the AED. The number and percentage of subjects taking concomitant AEDs will be summarized by preferred drug name for the Safety Set.

6.5 Potential drug-induced liver injury (PDILI)

Subjects with potential drug-induced liver injury (PDILI) will be assessed to determine if IMP must be discontinued. If PDILI occurs, additional lifestyle and family medical history information will be collected. The number and percentage of subjects with PDILI using laboratory criteria will be summarized. Listings of lifestyle and family medical history will be provided for subjects with PDILI.

Change #26

7 MEASUREMENTS OF TREATMENT COMPLIANCE

7.1 Treatment compliance and modifications

Study drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of study drug as instructed. The number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed.

The study drug compliance (%) for each visit will be calculated by dividing the total number of tablets taken up to the next visit by the total number of tablets prescribed at each visit and then multiplying by 100. The overall study drug compliance (%) will be calculated by dividing the total number of tablets taken at all visits by the total number of tablets prescribed for all visits and then multiplying by 100. [Example: Compliance (%) = [(total no. of tablets dispensed – total no. of tablets returned) / (No. of days in visit interval *No. of tablets prescribed per day)] * 100]. It is assumed that half of the daily dose should be consumed on the first day and last day of a duration of administration.

The study drug compliance will be summarized by study group and study period using the descriptive statistics. For the Evaluation Period, the statistics will be calculated not only overall but also by 3-month period.

Summary statistics on percentage of treatment compliance as well as the number and percentage of subjects in each compliance category (<80%, 80-120% and greater than 120% compliant) will be presented with the same specification stated above. Percentages will be calculated out of the number of subjects who were dosed at that dosing period.

Has been changed to:

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug compliance will not be assessed due to the complexities associated with the calculation and interpretation of study drug compliance for this study. Study drug dosing will be provided in subject data listings.

Change #27

8 EFFICACY ANALYSES

All efficacy outcomes will be summarized with descriptive statistics only on the FAS.

Has been changed to:

8 EFFICACY ANALYSES

All efficacy outcomes <u>for all study periods</u> will be summarized with descriptive statistics only on the FAS. <u>All efficacy analyses to the Evaluation Period will be based on the seizure records during the Evaluation Period on/after the first dose of BRV.</u>

Change #28

8.1.2 Percent reduction of 28-day adjusted partial seizure frequency

Percent reduction of 28DPSF is defined as the percentage reduction of 28DPSF at post-baseline point compared with the baseline 28DPSFduring the Evaluation Period. This variable will be derived as following equation:

$$\text{Percent reduction} = \frac{\text{Baseline 28DPSF} - \text{Post Baseline 28DPSF}}{\text{Baseline 28DPSF}}$$

Has been changed to:

Percent reduction of 28DPSF is defined as the percentage reduction of 28DPSF for a designated post-baseline period compared with the Baseline 28DPSF. This variable will be derived as following equation:

$$\text{Percent reduction} = \frac{\text{Baseline 28DPSF} - \text{Post Baseline 28DPSF}}{\text{Baseline 28DPSF}} \times 100$$

For rollover subjects the Baseline seizure will be obtained from EP0083 and N01358 study. For direct enrollers, the Baseline seizure counts will be collected from 8 weeks prior to the first BRV administration (see section 3.3) and the number of days during the Baseline Period will be set as 56 days.

Change #29

8.1.4 Seizure free

A subject is defined as seizure free during the Evaluation Period if they meet all of the following criteria:

- Criteria 1: the subject completed the Evaluation Period
- Criteria 2: the subject did not have more than 90% missing diary days during the Evaluation Period
- Criteria 3: the subject did not report any seizures during the Evaluation Period

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

- Criteria 1: A subject who completed study or were converted to commercial BRV is defined as completing the Evaluation Period if End of Study Visit is completed. A subject who discontinued study is defined as completing the Evaluation Period if EDV is completed.
- Criteria 2: A subject who meet the criteria 2 is defined as if more than 90% of the seizure diary was completed from the day after Visit 1 up to the day prior to the end date of the Evaluation Period.
- Criteria 3: A subject who meets criteria 3 is defined as if there are no diary records from the day after Visit 1 up to and including the end date of the Evaluation Period with either a count >0 or a reported seizure code with an unknown or missing seizure count.

Has been changed to:

8.1.4 Seizure freedom (partial, all epileptic seizure)

A subject is defined as seizure free for a designated period during the Evaluation Period if they meet all of the following criteria:

- Criteria 1: the subject completed the designated period during the Evaluation Period
- Criteria 2: the subject has at least 90% non-missing diary days during the period of time
- Criteria 3: the subject did not report any seizures during the period

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

~~• Criteria 1: A subject who completed study or were converted to commercial BRV is defined as completing the Evaluation Period if End of Study Visit is completed. A subject who discontinued study is defined as completing the Evaluation Period if EDV is completed.~~

~~• Criteria 2: A subject who meet the criteria 2 is defined as if more than 90% of the seizure diary was completed from the day after Visit 1 up to the day prior to the end date of the Evaluation Period.~~

~~• Criteria 3: A subject who meets criteria 3 is defined as if there are no diary records from the day after Visit 1 up to and including the end date of the Evaluation Period with either a count >0 or a reported seizure code with an unknown or missing seizure count.~~

Change #30

8.2.4 Analysis of seizure free

Based on the definition of seizure free in the Section 8.1.4, the parameters in the following sub-sections will be analyzed respectively.

8.2.4.1 The percentage of subjects continuously seizure-free

The below variables will be summarized as categorical parameters by study group:

- The number and percentage of subjects who have been continuously seizure-free for partial seizure by 3-month periods over the Evaluation Period
- The number and percentage of subjects who have been continuously seizure-free for all seizure types by 3-month periods over the Evaluation Period

The denominator of percentage for every 3-month period will be based on the total number of subjects for whom seizure assessment during the every 3-month period were performed satisfying the criteria 1 and 2 in 8.1.4.

- The number and percentage of subjects who have been continuously partial seizure-free at least 6 months during the Evaluation Period
- The number and percentage of subjects who have been continuously partial seizure-free at least 12 months during the Evaluation Period
- The number and percentage of subjects who have been continuously all types seizure-free at least 6 months during the Evaluation Period
- The number and percentage of subjects who have been continuously all types seizure-free at least 12 months during the Evaluation Period

The percentage for above four variables will be based on the FAS.

Has been changed to:

8.2.4 Analysis of seizure freedom

Based on the definition of seizure free in the Section 8.1.4, the parameters in the following sub-sections will be analyzed respectively.

8.2.4.1 The percentage of subjects continuously seizure-free

~~The below variables will be summarized as categorical parameters by study group:~~

~~• The number and percentage of subjects who have been continuously seizure-free for partial seizure by 3-month periods over the Evaluation Period~~

~~• The number and percentage of subjects who have been continuously seizure-free for all seizure types by 3-month periods over the Evaluation Period~~

~~The denominator of percentage for every 3-month period will be based on the total number of subjects for whom seizure assessment during the every 3-month period were performed satisfying the criteria 1 and 2 in 8.1.4.~~

- The number and percentage of subjects who have been continuously partial seizure-free at least 6 months during the Evaluation Period
- The number and percentage of subjects who have been continuously partial seizure-free at least 12 months during the Evaluation Period
- The number and percentage of subjects who have been continuously all types seizure-free at least 6 months during the Evaluation Period
- The number and percentage of subjects who have been continuously all types seizure-free at least 12 months during the Evaluation Period

The percentage for above four variables will be based on the FAS.

Change #31

8.2.4.2 Proportion of seizure-free days

The proportion of seizure-free days for partial seizure by 3-month periods over the Evaluation Period will be calculated based on the following equation:

Proportion of partial seizure free days (%)=(Partial seizure free days during 3 months)/(Total days during 3 months)×100

For the seizure-free days for all seizure types by 3-month periods over the Evaluation Period will be calculate as:

Proportion of all types seizure free days (%)=(All seizures free days during 3 months)/(Total days during 3 months)×100

The proportion of seizure-free days for partial seizure and all seizure types will be summarized by descriptive statistics by study group. The analysis time durations will be 3-month periods over the Evaluation Period.

In addition, the total days of partial seizure-free and all seizure types over the Evaluation Period will be summarized by 3-month periods and for the overall period.

The time to the first partial seizure and all types seizure will be presented graphically in Kaplan-Meier plots by study group during the Evaluation Period. In the analyses, first partial

seizure and all types seizure will be analyzed as events and discontinuation (or data-cutoff) during the period and completion of the period will be treated as censors. The duration (days) of partial seizure-free and all types seizure-free will be presented in box plots by study group during the Evaluation Period.

Has been changed to:

The analysis of proportion of seizure-free days has been removed since it is not included in the protocol.

Change #32

8.2.4.3 Subject with Seizure Freedom

The number and percentage of subjects who have been any types seizure-free over the Evaluation Period will be summarized by 3-month periods and overall period by study group.

Additionally, as a sensitivity analysis, the number and percentage of subjects meeting criteria 2 and 3 but not meeting criterion 1 will be summarized by 3-month periods and overall period by study group.

Has been changed to:

8.2.4.2 Subject with Seizure Freedom

The number and percentage of subjects who have been any types seizure-free over the Evaluation Period will be summarized ~~by 3-month periods and overall period~~ by study group.

Additionally, as a sensitivity analysis, the number and percentage of subjects meeting criteria 2 and 3 but not meeting criterion 1 will be summarized by 3-month periods and overall period by study group.

Change #33

9.1.1 Study drug duration

Duration of exposure to study drug is defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dose date (Day 1) to the last dose date as recorded on the Study Termination/Early Discontinuation page on the CRF. If the last dose date on the Study Termination/Early Discontinuation page is missing or a subject is lost to follow-up, but the drug accountability log confirms that the subject has taken study drug, the visit date following the last completed drug accountability log will be used. Days under the study drug exposure will be calculated as date of last dose minus date of first dose plus one.

The duration of exposure to study drug will be summarized by study group for all subjects in the SS and will be presented in a table by summary statistics. Total time at risk is defined as the total subject-years during the study. Total study drug duration is a subset of total time at risk excluding non-treated periods. The total time at risk and the total study drug duration of subject-year will be summarized.

Has been changed to:

Duration of exposure to study drug is defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dose date of EP0085 to the last dose date during the Treatment Period (i.e., last dose of study drug minus the date of first dose of study drug plus 1 day). If the last dose date on the Study Termination/Early Discontinuation page is missing or a subject is lost to follow-up, but the drug accountability log confirms that the subject has taken study drug, the visit date following the last completed drug accountability log will be used. Days under the study drug exposure will be calculated as date of last dose minus date of first dose plus one.

The duration of exposure to study drug will be summarized by study group for all subjects in the SS and will be presented in a table by summary statistics. ~~Total time at risk is defined as the total subject-years during the study. Total study drug duration is a subset of total time at risk excluding non-treated periods. The total time at risk and the total study drug duration of subject-year will be summarized.~~

Change #34

9.1.2 Study drug dose

The total cumulative dose will be defined as the sum of the doses across all study days. The mean daily dose is cumulative dose divided by total days on study. The mean daily dose and modal dose will be summarized using descriptive summary statistics by study group and study period.

A summary of each subject's exposure will be presented in a listing.

Has been changed to:

9.1.2 Study drug dose

The total cumulative dose will be defined as the sum of the doses across all study days. The mean daily dose is defined as cumulative dose divided by total days on study.

The modal daily dose will be calculated across all study days on or after the day of first dose of BRV and up to and including the day of last dose of BRV. Modal daily dose is the most frequently taken daily dose during this period. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as follows:

Category	Definition
5 mg/day	<20mg/day
20mg/day	≥20mg/day to <50mg/day
50mg/day	≥50mg/day to <100mg/day
100mg/day	≥100mg/day to <150mg/day
150mg/day	≥150mg/day to <200mg/day
200mg/day	≥200mg/day

The mean daily dose, modal daily dose, and modal daily dose category will be summarized using descriptive summary statistics by study group and study period.

A summary of each subject's exposure will be presented in a listing.

Change #35

9.2.1 Definition of treatment-emergent adverse events

AEs will be classified as either pre-study or treatment-emergent. Pre-study AEs are defined as AEs which had onset prior to the date of the first dose of BRV. Treatment-emergent AEs (TEAEs) are defined as AEs that had onset on or after the day of first BRV dose.

Has been changed to:

9.2.1 Definition of treatment-emergent adverse events

AEs will be classified as either pre-study or treatment-emergent. Pre-study AEs are defined as AEs which had onset prior to the date of the first dose of BRV in EP0085 study. Treatment-emergent AEs (TEAEs) are defined as AEs that had onset on or after the day of first BRV dose in EP0085 study. 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 the month and year of the first BRV dose or the year of onset (when only year is specified) is the same as the year of first BRV dose.

Change #36

9.2.2 Analysis of the primary safety variables

An overview summary of the number and percentage of subjects with any TEAEs, serious TEAEs, subject discontinuations due to TEAEs, permanent withdrawal of study medication due to TEAEs, TEAEs requiring dose change, drug-related TEAEs, severe TEAEs, all deaths (AEs leading to death), and deaths (TEAEs leading to death) will be provided by study group.

Has been changed to:

9.2.2 Summaries of TEAEs

Pre-study AEs will be provided in a subject data listing; no summary of pre-treatment AEs are planned. Summaries will be for TEAEs and will be provided overall by combining Evaluation Period, Down-Titration Period, and Study Drug-Free Period unless otherwise indicated.

The following summary of TEAEs will be provided:

- Incidence of TEAEs – overview

The following summaries of TEAEs will be provided by MedDRA SOC and PT:

- Incidence of TEAE (overall and by study periods)
- Incidence of TEAEs by safety time interval (overall)

- Incidence of TEAEs above reporting threshold of 5% of subjects (overall)
- Incidence of non-serious TEAEs above reporting threshold of 5% of subjects (overall)
- Incidence of TEAEs by maximum intensity (overall and by study periods)
- Incidence of TEAEs by maximum relationship (overall and by study periods)
- Incidence of TEAEs leading to permanent discontinuation of study drug (overall and by study periods)
- Incidence of treatment-emergent SAE (overall and by study periods)
- Incidence of TEAEs of special interest (overall and by study periods)
- Incidence of TEAEs requiring dose change (overall and by study periods)
- Incidence of TEAEs related to COVID-19 vaccination (overall and by study periods)

A subject is included in a 3 month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval as the nominator.

Change #37

9.2.2.1 Incidence of Adverse Events

Summaries of the total number of TEAEs and number and percentage of subjects with at least one TEAE will be provided by study group. TEAEs will be presented by SOC and PT. The incidence of TEAEs table will include the number and percentage of subjects and number of events by SOC and PT. For the number of subjects by PT, if a subject experiences the same PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. As with the PT, for the number of subjects by SOC, if a subject experiences multiple AEs within the same SOC during the period, then that SOC will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects at risk in the SS. The number of events at each level of SOC and PT will also be summarized.

A summary of AEs will also be presented in descending order from the SOC with the highest total incidence (that is, summed across all study groups) to the SOC with the lowest total incidence by study group. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order of total incidence.

In addition, a table for incidence of TEAEs per 100 subject-years will be provided.

All TEAEs will be presented in a listing with a glossary.

Has been changed to:

9.2.2.1 Incidence of adverse events

TEAEs will be presented by SOC and PT. The incidence of TEAE table will include the number and percentage of subjects and number of events by SOC and PT. For the number of subjects by PT, if a subject experiences the same PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. As with the PT, for the number of subjects by SOC, if a subject experiences multiple AEs within the same SOC during the period, then that SOC will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects in the SS. The number of events at each level of SOC and PT will also be summarized.

The summary of AEs will be presented in alphabetical order by SOC. Within each SOC, PTs will be sorted by descending order of total frequency (ie, frequency across all study groups) . If the total frequency for any two or more PTs is equal within a SOC, the PTs will be presented in alphabetical order.

A subject is included in a 3 month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval as the nominator.

A table for incidence of non-serious TEAEs above reporting threshold of 5% of subjects will be provided in the same manner.

The above summaries will be based on all TEAEs and additionally summaries of the incidence of TEAEs would be provided for each of the Evaluation, Down-Titration, and Study Drug-Free Periods.

All TEAEs will be presented in a listing with a glossary.

Change #38

9.2.2.5 Relationship of Adverse Events to Study drug

A summary of TEAEs by relationship to study drug will be presented in a table by incidence of occurrence. The relationships will be collected as the possibility that the study drug caused the event. The possible relationships are “Related” and “Not Related. In the AE relationship table, if a subject experiences multiple occurrences within each SOC and PT during that period, each subject is counted once according to the maximum relationship for all TEAEs within that SOC or PT. AE that is missing relationship will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of subjects at risk in the SS.

The AE data will be categorized and presented by SOC, PT and relationship in a manner similar to that described in the Section 9.2.2.1.

Has been changed to:

9.2.2.5 Relationship of adverse events to study drug

~~A summary of TEAEs by relationship to study drug will be presented in a table by incidence of occurrence. The relationships will be collected as the possibility that the study drug caused the event.~~ The possible relationships of TEAE are "Related" and "Not Related. ~~In the TEAE by relationship table,~~ If a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted separately according to each relationship to study drug within that SOC or PT.

In the TEAE by maximum relationship table, if a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted only once according to the maximum relationship to study drug within that SOC or PT.

AEs with missing relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship.

Percentages will be calculated out of the number of subjects in the SS.

The AE data will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

Change #39

9.2.2.6 Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are "Mild", "Moderate", and "Severe". In the AE severity table, if a subject reported multiple occurrences of the same AE, only the most severe will be presented. AEs that are missing severity will be presented on tables as "Severe" but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects at risk in the SS.

The AE data will be categorized and presented by SOC, PT and severity in a manner similar to that described in the Section 9.2.2.1.

Has been changed to:

9.2.2.6 Intensity of adverse event

Summary of TEAEs will be presented by intensity and maximum intensity:

~~In the TEAE by intensity table,~~ If a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted separately according to each intensity within that SOC or PT.

In the TEAE by maximum intensity table, if a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted only once according to the maximum intensity within that SOC or PT (severe > moderate > mild).

AEs with missing intensity will be presented on tables as "Severe" but will be presented in the data listing with a missing intensity. Percentages will be calculated out of the number of subjects in the SS.

The AE data will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

Change #40

A new section 9.2.2.8 regarding the adverse events related to COVID-19 vaccination is added:

9.2.2.8 Adverse events related to COVID-19 vaccination

The TEAE related to COVID-19 vaccination, which will be captured on the CRF page, will be categorized and presented by SOC and PT in a manner similar to that described in the Section 9.2.2.1.

Change #41

9.3.1.1 Hematology Biochemistry and Urinalysis parameters

All summaries will be based on the standard international units.

The observed values and change from baseline will be presented descriptively for hematology and biochemistry assessments with numeric values by study group for each scheduled visit and for Last Value. Change from baseline will be presented for each scheduled post-baseline visit and Last Value.

Outcomes from the clinical laboratory tests which will be classified as Low, Normal, or High according to the reference ranges will be summarized in shift tables comparing those at the extreme (either minimum or maximum) post-baseline value with those at the baseline value.

For the qualitative urinalysis parameters, the number and percentage of subjects with each response category will be summarized for Baseline, scheduled visits and Last Value. Additionally, this ordered categorical data will be summarized with shift tables in the same manner as stated above.

…

Has been changed to:

9.3.1.1 Hematology Biochemistry and Urinalysis parameters

All summaries will be based on the standard international units.

The observed values and change from baseline will be presented descriptively for hematology and biochemistry assessments with numeric values by study group for each scheduled visit and for Last Value. Change from baseline will be presented for each scheduled post-baseline visit and Last Value.

~~Outcomes from the clinical laboratory tests which will be classified as Low, Normal, or High according to the reference ranges will be summarized in shift tables comparing those at the extreme (either minimum or maximum) post-baseline value with those at the baseline value.~~

For the qualitative urinalysis parameters, the number and percentage of subjects with each response category will be summarized for Baseline, scheduled visits and Last Value. ~~Additionally, this ordered categorical data will be summarized with shift tables in the same manner as stated above.~~

…

Change #42

9.3.4 Electrocardiograms (ECG)

As for the reported ECG parameters, the observed values and change from baseline will be presented descriptively by study group for each scheduled visit and for Last Value.

Categorical analyses with appropriate classification in accordance with ICH E14 guidance will be conducted.

For the result of ECG abnormality, the number and percentage of subjects will be summarized for each scheduled visit and Last Value by study group. Additionally, shift table of Last Value versus baseline will be provided.

A listing of subjects will be provided, in which details of abnormality and ECG reader (investigator or cardiologist) will be included.

Has been changed to:

9.3.4 Electrocardiograms (ECG)

As for the reported ECG parameters, the observed values and change from baseline will be presented descriptively by study group for each scheduled visit and for Last Value.

~~Categorical analyses with appropriate classification in accordance with ICH E14 guidance will be conducted.~~

~~For the result of ECG abnormality~~ 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 Baseline, each visit during the Evaluation Period for which an ECG is scheduled to be performed, and Last Value. Percentages will be relative to the number of subjects with an ECG assessment at each time point. Same summary will be provided to ECG classification of QTc.

A listing of subjects will be provided, in which details of abnormality and ECG reader (investigator or cardiologist) will be included.

Change #43

9.3.5 Physical examination

A standard physical examination will be performed at time points specified in the protocol. Clinically significant new

Has been changed to:

9.3.5 Physical examination

A standard physical examination will be performed at time points specified in the protocol. No summaries of physical examination are planned because clinically significant new or worsened abnormalities will have to be reported as AEs.

Change #44

The following possibly clinically significant treatment-emergent (PCST) criteria are newly added to the section 12 Appendices:

Table 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

Table 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
Systolic Blood Pressure (mmHg)	<6m	<60, >100
	6m - <3y	<70, >120
	3y - <12y	<80, >140

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
	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

13.2 Amendment 2

Rationale for the amendment

The main purpose of this amendment is to remove the China subgroup analysis and to achieve consistency with other SAPs of the program.

Modifications and changes

Specific changes

Change #1

2.2.2 Efficacy variables

…

Efficacy variables for all subjects (rollovers in China and Japan and direct enrollers in Japan):

- Percentage of subjects continuously seizure-free for partial seizure for at least 6 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for partial seizure for at least 12 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for all seizure types (partial, generalized and unclassified epileptic seizure) for at least 6 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for all seizure types (partial, generalized and unclassified epileptic seizure) for at least 12 months during the Evaluation Period

Has been changed to:

2.2.2 Efficacy variables

…

Efficacy variables for all subjects (rollovers in China and Japan and direct enrollers in Japan):

- Percentage of subjects continuously seizure-free for partial seizure**s** for at least 6 months and at least 12 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for all seizure types (partial, generalized and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period

Change #2

2.3 Study design and conduct

…

In Japan and China, EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

Has been changed to:

2.3 Study design and conduct

…

In Japan ~~and China~~, EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

Change #3

The following new paragraph is added to section 3.1 General presentation of summaries and analyses:

For the analysis purposes, "core study" in this plan refers to the study where the subjects were firstly enrolled. For rollover subjects, the core study is N01358 (for rollover subjects from N01379) or EP0083 (for rollover subjects from EP0083). For direct enrollers EP0085 is the core study.

Change #4

3.2.4 Entry Visit

For rollover subjects from EP0083 and N01379, the following assessments will be completed during the last visit of the previous study and do not need to be repeated at Visit 1 (EV):

Has been changed to:

3.2.4 Entry Visit

The EV corresponds to the assessments performed at the time of entry into EP0085. For direct enrollers in Japan, the EV will be performed at Visit 1 and the relevant assessments will be performed according to the study protocol. For rollover subjects from EP0083 and N01379, the following assessments will be completed during the last visit of the previous study and do not need to be repeated at Visit 1 ~~(EV)~~:

Change #5

3.2.5 Study periods

Baseline Period	For rollover subjects from EP0083, the Baseline Period is defined as study days on or after EP0083 Visit 1 date and prior to EP0083 Visit 3 date. For rollover subjects from N01379, the Baseline Period is defined as study days on or after N01358 Visit 1 date and prior to N01358 Visit 3 date. For direct enrollers, the Baseline Period is defined as study days on or after EP0085 Visit 0 date and prior to EP0085 Visit 1 date.

Has been changed to:

3.2.5 Study periods

Baseline Period	For rollover subjects from EP0083, the Baseline Period corresponds to the Baseline Period of EP0083 and is defined as study days on or after EP0083 Visit 1 date and prior to EP0083 Visit 3 date. For rollover subjects from N01379, the Baseline Period corresponds to the Baseline Period of N01379 and is defined as study days on or after N01358 Visit 1 date and prior to N01358 Visit 3 date. For direct enrollers, except for seizure outcome the Baseline Period is defined as study days on or after EP0085 Visit 0 date and prior to EP0085 Visit 1 date. The Baseline Period for seizure outcome is defined as 8 weeks prior to the first BRV administration (see section 8.1.2).

Change #6

3.2.5 Study periods

Study Drug-Free Period (2 weeks)	… A subject is considered entering the Study Drug-Free Period if the subject has at least 1 contact (scheduled visit, unscheduled visit, or telephone contact) after the date of last dose of BRV. The 2-week Study Drug-Free Period starts 1 day after the date of last dose of BRV and ends on the date of Final Visit. For complete / discontinued subjects who do not enter the Down-Titration Period, the Study Drug-Free Period starts 1 day after the last dose of BRV and ends on the date of Final Visit.

Has been changed to:

3.2.5 Study periods

Study Drug-Free Period (2 weeks)	… A subject is considered entering the Study Drug-Free Period if the subject has at least 1 contact (scheduled visit, unscheduled visit, or telephone contact) after the date of last dose of BRV. The 2-week Study Drug-Free Period starts 1 day after the date of last dose of BRV and ends on the date of Final Visit, irrespective of entering the Down-Titration Period.

~~For complete / discontinued subjects who do not enter the Down-Titration Period, the Study Drug-Free Period starts 1 day after the last dose of BRV and ends on the date of Final Visit.~~

Change #7

3.2.5 Study periods

…

A subject is considered as completed if this subject completes all scheduled visits as defined in the protocol or convert to commercial BRV.

Has been changed to:

…

A subject is considered as completed if this subject completes all scheduled visits as defined in the protocol or converts to commercial BRV without a Down-Titration Period (where commercial BRV is available).

Change #8

3.2.6 Monthly time intervals

In terms of the analysis, a month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days). The following definitions of 3-month and 6-month intervals are based on 30-day months where the date of first dose of BRV is Day 1:

Interval	Duration Definition
Month 1-3	Day 1-90
Month 4-6	Day 90-180
Month 7-9	Day 181-270
Month 10-12	Day 271-360
Month 13-15	Day 361-450
Month 16-18	Day 451-540
Month 19-21	Day 541-630
Month 22-24	Day 631-720
Month 1-6	Day 1-180
Month 7-12	Day 181-360
Month 13-18	Day 361-540
Month 19-24	Day 541-720

Has been changed to:

3.2.6 Monthly time intervals

In terms of the analysis, a month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days). The following definitions of 3-month ~~and 6-month~~ intervals are based on 30-day months where the date of first dose of BRV is Day 1:

Interval	Duration Definition
3-month interval	
Month 1-3	Day 1-90
Month 4-6	Day 91-180
Month 7-9	Day 181-270
Month 10-12	Day 271-360

Subsequent 3-month intervals are defined in a similar manner. Three-month intervals will be used for analyses of efficacy (except for continuously seizure-free) and TEAE summaries.

For the analysis of efficacy outcomes, a subject is included in the analysis of a 3-month interval if the last dose of study drug during the Evaluation Period of EP0085 is equal or greater than the last day of the 3-month time interval and the seizure diary was completed for at least 1 day during the 3-month interval over the Evaluation Period.

For TEAE summaries, a subject is included in the analysis of a 3-month interval if the last dose of study drug in whole period of EP0085 is equal or greater than the first day of the 3-month time interval (as N for the time interval) and with at least one specified TEAE within the 3-month interval (as n in the summary tables according to the AE onset date).

Change #9

3.3 Definition of Baseline values

For rollover subjects, the baseline value for all safety and efficacy variables is defined as the last non-missing data collected prior to the first dose of study medication in study EP0083 or N01358, unless addressed otherwise for a specific type of data.

Has been changed to:

3.3 Definition of Baseline values

Unless otherwise specified, Baseline for all safety and efficacy variables will be based on baseline of the core study.

For rollover subjects, the baseline value for all safety and efficacy variables is defined as the last non-missing data collected prior to the first dose of study medication in the core study (EP0083 or N01358,), unless addressed otherwise for a specific type of data. Baseline seizure frequency will be obtained from the core study (EP0083 or N01358).

Change #10

3.6 Treatment assignment and study groups

It is expected that subjects will receive treatment as assigned in accordance with the study design.

Rollover subjects from N01379, EP0083, and directly enrolled subjects need to be analyzed separately. For EP0083 a detailed segmentation by drug group is necessary. Unless otherwise specified, results will be presented for each grouping described below:

…

Has been changed to:

3.6 Treatment assignment and study groups

This is an uncontrolled study in which all subjects receive BRV in doses that are optimally adjusted for each subject. It is expected that subjects will receive treatment as assigned in accordance with the study design.

Rollover subjects from N01379, EP0083, and directly enrolled subjects need to be analyzed separately. For rollovers from EP0083 a detailed segmentation by randomized drug group in EP0083 is necessary. Unless otherwise specified, results will be presented for each grouping described below:

…

Change #11

3.6 Treatment assignment and study groups

…

For submission purpose, the subgroup tables and figures will be presented by Japan and China. In Japan subgroup tables and figures, the study groups will be presented in the same manner as overall. In China subgroup tables and figure, given that only the EP0083 rollover subjects will be enrolled from China, the study group will be presented as follows:

- EP0083 Placebo
- EP0083 BRV All
- All Subjects

Has been changed to:

3.6 Treatment assignment and study groups

…

For submission purpose, the subgroup tables and figures will be presented by Japan ~~and China~~. In Japan subgroup tables and figures, the study groups will be presented in the same manner as overall. ~~In China subgroup tables and figure, given that only the EP0083 rollover subjects will be enrolled from China, the study group will be presented as follows:~~

~~- EP0083 Placebo~~

~~- EP0083 BRV All~~

~~• All Subjects~~

Change #12

4.1 Handling of missing data

No rule for handling of missing data will be applied for this LTFU study. Safety and efficacy variables will be analyzed as available. Days with missing information will be ignored in the calculation of the seizure frequency.

Since subjects may drop out from the study at different times, results will be presented overall, by study period, and by 6-month period during the Evaluation Period.

Missing data related to AEs and seizure frequency will be assessed in the DEM prior to database lock or interim report to ensure an acceptable level of protocol compliance.

Has been changed to:

4.1 Handling of missing data

No rule for handling of missing data will be applied for this LTFU study. Safety and efficacy variables will be analyzed as available. Days with missing information will be ignored in the calculation of the seizure frequency.

Since subjects may drop out from the study at different times, selected summaries will be presented by time interval.

~~Missing data related to AEs and seizure frequency will be assessed in the DEM prior to database lock or interim report to ensure an acceptable level of protocol compliance.~~

Change #13

4.1 Handling of missing data

…

For the calculation of variables related to seizure frequency, the dates during participation in EP0118 will be considered as not done for the purpose of efficacy analyses for trial EP0085 (eg, these dates will not be considered as days evaluated for seizure frequency). Due to the short nature of the EP0118 study, only a few days of seizure frequency data are expected to be missing due to participation in EP0118 unless otherwise specified (eg, for the evaluation of seizure freedom).

Has been changed to:

4.1 Handling of missing data

…

For the calculation of variables related to seizure frequency, the dates during participation in EP0118 will be considered as not done for the purpose of efficacy analyses for ~~trial~~ EP0085 according to the Seizure Count form entry (eg, these dates will not be considered as days evaluated for seizure frequency). ~~Due to the short nature of the EP0118 study, only a few~~

~~days of seizure frequency data are expected to be missing due to participation in EP0118 unless otherwise specified (eg, for the evaluation of seizure freedom).~~

Change #14

4.2 Interim analyses and data monitoring

No formal interim analysis is planned. However, data will be reported prior to the completion of this study to support regulatory submissions. At a minimum, 2 interim reports are planned after required number of ongoing subjects have completed Visit 5 (Week 24) and after required number of ongoing subjects have completed Visit 7 (Week 48).

Has been changed to:

4.2 Interim analyses and data monitoring

No formal interim analysis is planned. However, data will be reported prior to the completion of this study to support regulatory submissions. At a minimum, 2 interim reports are planned after ~~required number of~~ all ongoing subjects have completed Visit 5 (Week 24) and after required number of ongoing subjects have completed Visit 7 (Week 48). There are no statistical concerns with such interim reports for this open-label LTFU study.

Change #15

5.1 Subject disposition

… The summary of subjects in the SS who discontinued the study due to AE will be presented in a separate table. The percentages will be based on the number of patients in the SS.

Has been changed to:

5.1 Subject disposition

… The summary of subjects in the SS who discontinued the study due to AE will be presented in a separate table. ~~The percentages will be based on the number of patients in the SS.~~

Change #16

5.2 Protocol deviations

…

The assignment of subjects to each of the analysis sets will be listed for all subjects enrolled. In addition, the reasons for exclusion will be provided in the listing.

Has been changed to:

5.2 Protocol deviations

…

The assignment of subjects to each of the analysis sets will be listed for all subjects enrolled. ~~In addition, the reasons for exclusion will be provided in the listing.~~

Change #17

6 CHARACTERISTICS

All summaries for subject characteristics will be based on SS.

Has been changed to:

6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All summaries for subject characteristics will be based on SS. Unless otherwise specified, all demographics and other baseline characteristics summaries will be based on data collected in the core study.

Change #18

6.1 Demographics

Age will be calculated based on the date of informed consent and date of birth. The result will be kept as integer and the unit of age is years.

A birth date of each subject provided from the feeder studies is imputed to be born on the first day of that month (yyyy-mm-01).

The demographic variables will be listed by subject.

Has been changed to:

6.1 Demographics

Age will be calculated based on the date of informed consent in EP0085 and date of birth. The result will be kept as integer and the unit of age is years. A birth date of each subject provided from the core studies is imputed to be born on the first day of that month (yyyy-mm-01). Except for age, all other demographic variables will be based on data from baseline of core study.

~~A birth date of each subject provided from the feeder studies is imputed to be born on the first day of that month (yyyy-mm-01).~~

The demographic variables will be listed by subject.

Change #19

6.2 History of epilepsy

The following epilepsy-related background variables will be summarized by study group:

- Vagus nerve stimulation (VNS) at Screening/Baseline
- History of epileptic seizures

- Classification of epileptic syndrome
- Baseline seizure type and partial seizure frequency

Has been changed to:

6.2 History of epilepsy

The following epilepsy-related background variables will be summarized by study group based on the Safety Set:

~~• Vagus nerve stimulation (VNS) at Screening/Baseline~~

~~• History of epileptic seizures~~

• Epileptic seizure profile: the number and percentage of subjects experiencing each seizure type at any time based on the Classification of Epileptic Seizures (ILAE,1981) prior to the core study entry will be summarized.

• History of epileptic seizures at the core study: the number and percentage of subjects with a history of status epilepticus and quantitative summaries of epilepsy duration, age at time of first diagnosis of seizure, and percent of life with epilepsy, will be summarized. Percent of life with epilepsy will be calculated as 100 times epilepsy duration relative to the first diagnosis date and divided by the subject's age at the core study entry.

• Classification of epileptic syndrome collected at the core study: the number and percentage of subjects with each epileptic syndrome will be summarized.

• Baseline seizure type and partial seizure frequency collected at the core study: the number and percentage of subjects who experienced each seizure type during the Baseline Period of core study will be presented. 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 of core study.

Change #20

6.4 Prior and concomitant medications

All prior and concomitant medications will be coded according to the WHODD version September 2017. The AED is defined according to the list of antiepileptic drug as indicated in Appendix 3 of the study protocol.

Has been changed to:

6.4 Prior and concomitant medications

All prior and concomitant medications will be coded according to the WHODD version September 2017. ~~The AED is defined according to the list of antiepileptic drug as indicated in Appendix 3 of the study protocol.~~ Medications taken at study entry are the ongoing medications at the study entry of the core study. Previous medications are medications taken and discontinued prior to entry into the core study. Concomitant medications are medications taken during administration of BRV in EP0085 study. Previous AEDs and AED taken at core study entry will follow the AED definition according to the respective core study.

Change #21

6.4.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AEDs at study entry will be summarized for Safety Set by primary therapeutic group (Anatomic Therapeutic Class [ATC] level 1), therapeutic subgroup (ATC level 2), and preferred drug name for the Safety Analysis Set.

For rollover subjects the medications will be the non-AEDs taken at study entry of the previous feeder study and the information will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications " from N01358 (for subjects from N01378). For direct enrollers the medication will be the non-AEDs taken at study entry of EP0085 and the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

Has been changed to:

6.4.1 Non-AEDs taken at study entry

The number and percentage of subjects taking non-AEDs at study entry will be summarized for Safety Set by primary therapeutic group (Anatomic Therapeutic Class [ATC] level 1), therapeutic subgroup (ATC level 2), and preferred drug name ~~for the Safety Analysis Set~~.

Non-AED taken at study entry refers to the core study entry. The non-AEDs at core study entry will follow the AED definition according to the respective core study. For rollover subjects the ~~medications will be the non-AEDs taken at study entry of the previous feeder study and the information~~ will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications " from N01358 (for subjects from N01378). For direct enrollers ~~the medication will be the non-AEDs taken at study entry of EP0085 and~~ the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

Change #22

6.4.2 History of previous AED use

The number and percentage of subjects who had taken at least 1 previous AED will be summarized overall and by preferred drug name for the Safety Set. For rollover subjects the previous AEDs are AEDs taken and discontinued prior to entry into the previous feeder study and the information will be obtained from CRF form "History of Previous Antiepileptic Drug Treatment" from EP0083 and N01358 (for subjects from N01378). For direct enrollers the previous AEDs are AEDs taken and discontinued prior to EP0085 and the information will be obtained from EP0085 CRF form "History of Previous Antiepileptic Drug Treatment".

Has been changed to:

6.4.2 History of previous AED use

The number and percentage of subjects who had taken at least 1 previous AED prior to entry into the core study will be summarized overall and by preferred drug name for the Safety Set.

For rollover subjects ~~the previous AEDs are AEDs taken and discontinued prior to entry into the previous feeder study and~~ the information will be obtained from CRF form "History of Previous Antiepileptic Drug Treatment" from EP0083 and N01358 (for subjects from N01378). For direct enrollers ~~the previous AEDs are AEDs taken and discontinued prior to EP0085 and~~ the information will be obtained from EP0085 CRF form "History of Previous Antiepileptic Drug Treatment". Different with the core study N01358, for core study EP0083 (for the rollover subjects from EP0083) and EP0085 (for the direct enrollers), the history of previous AED was recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol, however, the Investigator's judgement was prioritized and taken into consideration.

Change #23

6.4.4 AEDs taken at study entry

The number and percentage of subjects taking AEDs at study entry visit will be summarized by preferred drug name for the Safety Set. For rollover subjects the medications will be the AEDs taken at study entry of the previous feeder study and the information will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications(AEDs only)" from N01358 (for subjects from N01378). For direct enrollers the medication will be the AEDs taken at study entry of EP0085 and the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

Has been changed to:

6.4.4 AEDs taken at study entry

The number and percentage of subjects taking AEDs at study entry visit will be summarized by preferred drug name for the Safety Set. ~~For rollover subjects the medications will be the~~

AED taken at study entry refers to the core study entry. The AEDs at core study entry will follow the AED definition according to the respective core study. Different with the core study N01358, for core study EP0083 (for the rollover subjects from EP0083) and EP0085 (for the direct enrollers), the AEDs taken at study entry was recorded in accordance with the list of AEDs as indicated in Appendix 3 of the study protocol and was captured according to the CRF "Core AED?" based on the Investigator's judgement.

For rollover subjects the information will be obtained from CRF form "Prior and Concomitant Medications (including AEDs)" from EP0083 and CRF form "Prior and Concomitant Medications (AEDs only)" from N01358 (for subjects from N01379). For direct enrollers the information will be obtained from EP0085 CRF form "Concomitant Medications (including AEDs)".

Change #24

6.4.5 Concomitant AEDs

A concomitant AED is an AED which was taken during administration of BRV in EP0085 study, regardless of the start and stop date of the AED. The number and percentage of subjects taking concomitant AEDs will be summarized by preferred drug name for the Safety Set.

Has been changed to:

6.4.5 Concomitant AEDs

A concomitant AED is an AED which was taken during administration of BRV in EP0085 study, regardless of the start and stop date of the AED. Concomitant AEDs 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. The number and percentage of subjects taking concomitant AEDs will be summarized by preferred drug name for the Safety Set.

Change #25

The following new section is added:

6.4.6 Vagus nerve stimulation (VNS)

For all subjects, the VNS information will be obtained from EP0085 CRF form: Vagus Nerve Stimulation Status at Screening/Baseline. The number and percentage of subject who had VNS at Screening/Baseline of EP0085 will be summarized in a table. A listing of VNS status at study entry and VNS setting at the subsequent visits will be provided.

Change #26

6.5 Potential drug-induced liver injury (PDILI)

Subjects with potential drug-induced liver injury (PDILI) will be assessed to determine if IMP must be discontinued. If PDILI occurs, additional lifestyle and family medical history information will be collected. The number and percentage of subjects with PDILI using laboratory criteria will be summarized. Listings of lifestyle and family medical history will be provided for subjects with PDILI.

Has been changed to:

6.5 Potential drug-induced liver injury (PDILI) related information

Subjects with potential drug-induced liver injury (PDILI) will be assessed to determine if IMP must be discontinued. If PDILI occurs, additional lifestyle and family medical history information will be collected. ~~The number and percentage of subjects with PDILI using laboratory criteria will be summarized.~~ Listings of lifestyle and family medical history will be provided if any subject reporting PDILI.

Change #27

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug compliance will not be assessed due to the complexities associated with the calculation and interpretation of study drug compliance for this study. Study drug dosing will be provided in subject data listings.

Has been changed to:

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug compliance will not be ~~assessed~~ calculated because the planned dose information is not collected and also due to the complexity associated with the calculation and interpretation of study drug compliance for this study. However, study drug compliance will be evaluated during the review of important protocol deviation. Study drug dosing will be provided in subject data listings.

Change #28

8 EFFICACY ANALYSES

All efficacy outcomes for all study periods will be summarized with descriptive statistics only on the FAS. All efficacy analyses to the Evaluation Period will be based on the seizure records during the Evaluation Period on/after the first dose of BRV.

Has been changed to:

8 EFFICACY ANALYSES

All efficacy outcomes ~~for all study periods~~ will be summarized with descriptive statistics only on the FAS. All efficacy analyses to the Evaluation Period will be based on the seizure records during the Evaluation Period on/after the first dose of BRV.

Change #29

8.1.2 Percent reduction of 28-day adjusted partial seizure frequency

Percent reduction of 28DPSF is defined as the percentage reduction of 28DPSF for a designated post-baseline period compared with the Baseline 28DPSF. This variable will be derived as following equation: …

Has been changed to:

8.1.2 Percent reduction of 28-day adjusted partial seizure frequency

Percent reduction of 28DPSF from Baseline is defined as the percentage reduction of 28DPSF for a designated post-baseline period in EP0085 compared with the Baseline 28DPSF in the core study. This variable will be derived as following equation: …

Change #30

8.2.3 Analysis for responder rate of 28DPSF

The number and percentage of responders will be summarized by study group. The summary will be presented by study visit and all over the Evaluation Period. The denominator of percentage will be based on the total number of subjects with at least 1 seizure assessment during the time interval. The numerator will be the number of responders.

Has been changed to:

8.2.3 Analysis for responder rate of 28DPSF

The number and percentage of responders will be summarized by study group. The ~~summary~~ analysis time intervals will be 3-month periods ~~presented by study visit and all~~ over the Evaluation Period. The denominator of percentage will be based on the total number of subjects with at least 1 seizure assessment during the time interval. The numerator will be the number of responders.

Change #31

8.2.4.1 The percentage of subjects continuously seizure-free

- The number and percentage of subjects who have been continuously partial seizure-free at least 6 months during the Evaluation Period
- The number and percentage of subjects who have been continuously partial seizure-free at least 12 months during the Evaluation Period
- The number and percentage of subjects who have been continuously all types seizure-free at least 6 months during the Evaluation Period
- The number and percentage of subjects who have been continuously all types seizure-free at least 12 months during the Evaluation Period

The percentage for above four variables will be based on the FAS.

Has been changed to:

8.2.4.1 The percentage of subjects continuously seizure-free

The number and percentage of subjects who have been continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period will be summarized.

In addition to the 6 months and 12 months of intervals of continuously seizure-free, subsequent 6-month intervals will be summarized in a similar manner.

The percentage of subjects with continuously seizure-free will be based on the number of subjects exposed to BRV for at least the specific time interval.

Change #32

8.2.4.2 Subject with Seizure Freedom

The number and percentage of subjects who have been any types seizure-free over the Evaluation Period will be summarized by study group.

Has been changed to:

8.2.4.2 Seizure Freedom

The number and percentage of subjects with seizure-freedom (partial, all epileptic seizure) during the Evaluation Period will be summarized by study group.

Change #33

9.1.1 Study drug duration

Duration of exposure to study drug is defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dose date of EP0085 to the last dose date during the Treatment Period (i.e., last dose of study drug minus the date of first dose of study drug plus 1 day). If the last dose date on the Study Termination/Early Discontinuation page is missing or a subject is lost to follow-up, but the drug accountability log confirms that the subject has taken study drug, the visit date following the last completed drug accountability log will be used. Days under the study drug exposure will be calculated as date of last dose minus date of first dose plus one.

The duration of exposure to study drug will be summarized by study group for all subjects in the SS and will be presented in a table by summary statistics.

The subject exposure duration will then be classified into one of the following categories: >0 month, ≥3 months, ≥6 months, ≥12 month, ≥18month, and ≥24 months and will be presented as the number and percentage of subjects in each duration category. Percentages will be computed based on the number of subjects in the SS.

Has been changed to:

9.1.1 Study medication duration and total study medication duration in subject-years

Duration of exposure to study medication is defined as the total number of days a subject is exposed to study medication and will be calculated as the date of last dose in EP0085 minus date of first dose in EP0085 plus one in days. If the last dose date on the Study Termination / Early Discontinuation page is missing the last dose date will be captured from the Drug Dosing Log CRF. Gaps in BRV treatment or days on the Drug Dosing Log CRF with unknown dosing and/or partial missing exposure date will not be subtracted from the total duration of exposure.

Total study medication duration in subject-years will be calculated as the total duration of exposure in days divided by 365.25.

The duration of exposure to study medication will be summarized by study group for all subjects in the SS and will be presented in a table by summary statistics.

The subject cumulative exposure duration will then be classified into one of the following categories: >0 month, ≥3 months, ≥6 months, ≥12 month, ≥18 month, ≥24 months, ≥ 36 months, ≥ 48 months, and so forth in 12-month increments up to the maximum duration of exposure and will be presented as the number and percentage of subjects in each duration category by BRV overall and by modal dose group. Percentages for BRV overall will be

computed based on the Safety Set. Percentages for the modal dose group will be computed based on the number of subjects exposed overall or within each duration of exposure.

Change #34

9.2.2 Summaries of TEAEs

…

The following summary of TEAEs will be provided:

- Incidence of TEAEs – overview

…

- Incidence of TEAEs by maximum relationship (overall and by study periods)
- Incidence of TEAEs leading to permanent discontinuation of study drug (overall and by study periods)

A subject is included in a 3 month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval as the nominator.

Has been changed to:

9.2.2 Summaries of TEAEs

…

The following summary of TEAEs will be provided:

- Incidence of TEAEs – overview (overall and by study periods)

…

- Incidence of TEAEs by ~~maximum~~ relationship (overall and by study periods)
- Incidence of TEAEs leading to permanent discontinuation of study drug (overall ~~and by study periods~~)
- Incidence of treatment-emergent SAE by relationship (overall)
- Incidence of fatal TEAEs by relationship (overall)

For by-study period summary tables, TEAEs will be attributed according to the onset date.

Three-month safety time interval will be used to summarize data up to and including the maximum duration of exposure to BRV. TEAEs which had onset prior to or on the date of the last dose of BRV are included in summaries by 3-month time intervals. A subject is included in a 3-month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-

month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval according to the onset date as the nominator.

Change #35

9.2.2.1 Incidence of adverse events

TEAEs will be presented by SOC and PT. The incidence of TEAE table will include the number and percentage of subjects and number of events by SOC and PT. For the number of subjects by PT, if a subject experiences the same PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. As with the PT, for the number of subjects by SOC, if a subject experiences multiple AEs within the same SOC during the period, then that SOC will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects in the SS. The number of events at each level of SOC and PT will also be summarized.

The summary of AEs will be presented in alphabetical order by SOC. Within each SOC, PTs will be sorted by descending order of total frequency (ie, frequency across all study groups). If the total frequency for any two or more PTs is equal within a SOC, the PTs will be presented in alphabetical order.

A subject is included in a 3-month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval as the nominator.

A table for incidence of non-serious TEAEs above reporting threshold of 5% of subjects will be provided in the same manner.

The above summaries will be based on all TEAEs and additionally summaries of the incidence of TEAEs would be provided for each of the Evaluation, Down-Titration, and Study Drug-Free Periods.

All TEAEs will be presented in a listing with a glossary.

Has been changed to:

9.2.2.1 Incidence of adverse events

TEAEs will be presented by SOC and PT. The incidence of TEAE table will include the number and percentage of subjects and number of events by SOC and PT. For the number of subjects by SOC/PT, if a subject experiences the same PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. ~~As with the PT, for the number of subjects by SOC, if a subject experiences multiple AEs within the same SOC during the period, then that SOC will only be incremented by one since subject counts will be presented.~~ Percentages will be calculated out of the number of subjects in the SS. The number of events at each level of SOC and PT will also be summarized.

The summary of AEs will be presented in alphabetical order by SOC. Within each SOC, PTs will be sorted by descending order of total frequency (ie, frequency across all study groups). If the total frequency for any two or more PTs is equal within a SOC, the PTs will be presented in alphabetical order.

~~A subject is included in a 3-month interval if the subject was receiving BRV at any time during that interval based on their duration of exposure to BRV (eg, a subject with exposure for 91 days is included in the time interval for Months 1-3 and Months 4-6). Summaries of AEs by 3-month intervals will include all subjects who are classified into each time interval as defined above as the denominator and TEAEs reported within the specific time interval as the nominator.~~

~~A table for incidence of non-serious TEAEs above reporting threshold of 5% of subjects will be provided in the same manner.~~

~~The above summaries will be based on all TEAEs and additionally summaries of the incidence of TEAEs would be provided for each of the Evaluation, Down-Titration, and Study Drug-Free Periods.~~

All TEAEs will be presented in a listing with a glossary.

Change #36

9.2.2.3 Occurrence of serious adverse events

Serious TEAEs will be presented in a table by SOC and PT in a manner similar to that described in the Section 9.2.2.1. The table of serious TEAEs will include only one occurrence of a PT per subject. If a subject experiences the same SAE PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. As with the PT, if a subject experience multiple SAEs within the same SOC, then that SOC will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects in the SS.

Has been changed to:

9.2.2.3 Occurrence of serious adverse events

Serious TEAEs will be presented in a table by SOC and PT in a manner similar to that described in the Section 9.2.2.1. ~~The table of serious TEAEs will include only one occurrence of a PT per subject. If a subject experiences the same SAE PT multiple times during the period, then that PT will only be incremented by one since subject counts will be presented. As with the PT, if a subject experience multiple SAEs within the same SOC, then that SOC will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects in the SS.~~

Change #37

9.2.2.5 Relationship of adverse events to study drug

The possible relationships of TEAE are "Related" and "Not Related. If a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted separately according to each relationship to study drug within that SOC or PT.

In the TEAE by maximum relationship table, if a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted only once according to the maximum relationship to study drug within that SOC or PT.

Has been changed to:

9.2.2.5 Relationship of adverse events to study drug

~~The possible relationships of TEAE are "Related" and "Not Related. If a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted separately according to each relationship to study drug within that SOC or PT.~~

~~In the TEAE by maximum relationship table, if a subject experiences multiple occurrences within the SOC and PT during that period, the subject is counted only once according to the maximum relationship to study drug within that SOC or PT.~~

The relationships of TEAE will be either "Related" or "Not Related" according to the CRF entry. AEs with missing relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship.

Change #38

9.3 Statistical analysis of the other safety variables

Has been changed to:

9.3 Other safety variables

Unless otherwise indicated baseline is defined as the last non-missing data collected prior to the first dose of study medication (including Placebo and BRV) in core study. Core study is defined as the first study a study participant was enrolled in.

Change #39

9.3.1.1 Hematology, biochemistry and urinalysis parameters

… The observed values and change from baseline will be presented descriptively for hematology and biochemistry assessments with numeric values by study group for each scheduled visit and for Last Value. Change from baseline will be presented for each scheduled post-baseline visit and Last Value.

…

Possibly clinically significant treatment-emergent (PCST) abnormalities for laboratory values will be summarized by visit and at Last Value as stated above. Additionally, it will be analyzed for the worst value which is either a minimum value for a downward criterion or a maximum value for an upward criterion. The PCST abnormality will also summarized with

shift tables of post-baseline results versus baseline results. Details of PCST criteria are available in Section 12.1.

Has been changed to:

9.3.1.1 Hematology, biochemistry and urinalysis parameters

… The observed values and change from baseline will be presented descriptively for hematology and biochemistry assessments with numeric values by study group for each scheduled visit and for Last Value. Change from baseline will be presented for each scheduled post-baseline visit and Last Value. Last Value is the last available assessment during treatment with BRV.

…

Possibly clinically significant treatment-emergent (PCST) abnormalities for laboratory values will be summarized by visit and at Last Value as stated above. ~~Additionally, it will be analyzed for the worst value which is either a minimum value for a downward criterion or a maximum value for an upward criterion.~~ The PCST abnormality will also summarized with shift tables of post-baseline results versus baseline results. Details of PCST criteria are available in Section 12.1.

Change #40

9.3.1.2 PDILI laboratory measurements

The number and percentage of subjects with PDILI will be summarized in table by study group for each scheduled visit and for Last Value. In addition, the number and percentage of subjects meeting ALT or AST or both, total bilirubin and symptoms criteria will be summarized in table.

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

Has been changed to:

9.3.1.2 PDILI laboratory measurements

The number and percentage of subjects with PDILI will be summarized in table by study group ~~for each scheduled visit and for Last Value~~. In addition, the number and percentage of subjects meeting ALT or AST or both, total bilirubin and symptoms criteria will be summarized in table.

Listings of subjects with PDILI include alcohol use within past 6 months, the laboratory results for ALT, AST and Total bilirubin, symptoms of hepatitis or hypersensitivity, action and follow up will be provided only if any subject reporting PDILI.

Change #41

9.3.2 Vital signs

The observed value and change from baseline for vital signs parameters will be presented at each scheduled visit and Last Value by study group.

PCST abnormalities for vital signs will be summarized as stated in Section 9.3.1.1.

Has been changed to:

9.3.2 Vital signs

The observed value and change from baseline for vital signs parameters will be presented at each scheduled visit and Last Value by study group.

~~PCST abnormalities for vital signs will be summarized as stated in Section 9.3.1.1.~~

The number and percentage of subjects with any PCST values, any PCST low values, and any PCST high value will be summarized. Percentages will be relative to the number of subjects with an assessment within each visit. Details of PCST criteria are available in Section 12.1.2

Change #42

9.3.5 Physical examination

A standard physical examination will be performed at time points specified in the protocol. No summaries of physical examination are planned because clinically significant new or worsened abnormalities will have to be reported as AEs.

Has been changed to:

9.3.5 Physical examination

A standard physical examination will be performed at time points specified in the protocol. No summaries of physical examination are planned because physical examination findings were not recorded on the CRF, and clinically significant new or worsened abnormalities will have to be reported as AEs.

Change #43

9.3.6 Neurological examination

A listing of abnormal neurological examination findings will be provided; no summaries of neurological examination findings are planned because clinically significant new or worsened abnormalities will have to be reported as AEs.

Has been changed to:

9.3.6 Neurological examination

A listing of abnormal neurological examination findings or examination that was not done will be provided; no summaries of neurological examination findings are planned because clinically significant new or worsened abnormalities will have to be reported as AEs.

13.3 Amendment 3

Rationale for the amendment

The main purpose of this amendment is to align the SAP with the Protocol Amendment 4.

Modifications and changes

Specific changes

Change #1

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 3 and Protocol Amendment 3.1 (Japan) and Case Report Form (CRF) version 8.0.

Has been changed to:

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 and Case Report Form (CRF) version 8.0.

Change #2

2.2.1.1 Primary safety variables
The primary safety variable is adverse events (AEs).

Has been changed to:

2.2.1.1 Primary safety variables
The primary safety variable is treatment-emergent adverse events (TEAEs).

Change #3

2.2.2 Efficacy variables
…
Efficacy variables for all subjects (rollovers in China and Japan and direct enrollers in Japan):

- Percentage of subjects continuously seizure-free for partial seizures for at least 6 months and at least 12 months during the Evaluation Period
- Percentage of subjects continuously seizure-free for all seizure types (partial, generalized and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

Has been changed to:

Efficacy variables for all subjects (rollovers in China and Japan and direct enrollers in Japan):

- Percentage of subjects continuously seizure-free for partial seizures and all seizure types (partial, generalized and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

Change #4

2.3 Study design and conduct

…

EP0085 will continue until the market approval of BRV or one year after each subject has entered into EP0085, or until the sponsor decides to close the study, whichever comes first. In the event that market approval is not obtained in the participant country, the subject will be able to continue in EP0085 for two years after entering EP0085.

In Japan, EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

At selected sites in Japan, Japanese subjects may participate in an additional study (EP0118) with the intravenous formulation of BRV without withdrawing from EP0085. Ten evaluable subjects are planned for EP0118, and the total duration in the study for each subject is 7 days. The study period of EP0118 will be included in that of EP0085. Subjects will continue to receive their current dose of BRV at the time of entry that will remain stable for the duration of EP0118. Subjects who complete or withdraw from EP0118 will be given the opportunity to resume their participation in EP0085 with oral BRV treatment. In the event that a subject withdraws from EP0118 and is required to taper off BRV, the subject will return to EP0085 and taper using BRV tablets. Adverse events and concomitant treatment(s)/medication(s) that occur or are administered during EP0118 will be recorded in EP0118. Ongoing AEs and concomitant medication(s)/medical procedure(s) originating from the EP0118 will be recorded and followed in EP0085 until resolution or until the status of AE and/or concomitant medications are stable. All other data reported for EP0118 will be captured in the EP0118 database. Per the EP0118 protocol, the study (EP0118) will require hospitalization. Hospitalization for study participation does not need to be reported as an SAE.

Has been changed to:

2.3 Study design and conduct

…

EP0085 will continue until the market approval of BRV ~~or one year after each subject has entered into EP0085,~~ or until the sponsor decides to close the study, whichever comes first. In the event that market approval is not obtained in the participant country, the subject will be able to continue in EP0085 for two years after entering EP0085.

In Japan, EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

At selected sites in Japan, Japanese subjects may participate in an additional study (EP0118) with the intravenous formulation of BRV without withdrawing from EP0085. Ten evaluable subjects are planned for EP0118, and the total duration in the study for each subject is 7 days. The study period of EP0118 will be included in that of EP0085. Subjects will continue to receive their current dose of BRV at the time of entry and it will remain stable for the duration of EP0118. Subjects who complete or withdraw from EP0118 will ~~be given the opportunity to~~ resume their participation in EP0085 with oral BRV treatment. In the event that a subject withdraws from EP0118 and is required to down-titrate BRV treatment, the subject will return to EP0085 and down-titrate using BRV tablets. TEAEs and concomitant treatment(s)/medication(s) that occur or are administered during EP0118 will be recorded in EP0118. Ongoing TEAEs and concomitant medication(s)/medical procedure(s) originating from EP0118 will be recorded and followed in EP0085 until resolution or until the status of the TEAE and/or concomitant medications are stable. All other data reported for EP0118 will be captured in the EP0118 database. Per the EP0118 protocol, the study (EP0118) will require hospitalization. Hospitalization for study participation does not need to be reported as an SAE.

Change #5

3.8 Changes to protocol-defined analyses
According to the Protocol Amendment 3 and Protocol Amendment 3.1 (Japan), the mental and psychiatric status are included as the other safety variables. However, both variables are not collected in EP0085 CRF. The relevant analysis will not be conducted.

Has been changed to:

3.8 Changes to protocol-defined analyses

Not applicable.

Change #6

The following new section is added:

6.6 Neuro-imaging procedure

A neuro-imaging procedure, including brain magnetic resonance imaging (MRI), brain computerized tomography (CT) scan or other imaging test will be performed for direct enrollers at Screening Visit per Investigator discretion. A listing of CT and MRI data will be provided.

Change #7

The following new section is added:

6.7 Electroencephalogram

For direct enrollers, if there is no appropriate EEG available within the last 10 years, a Baseline EEG must be scheduled at the SV and the results received before the EV. A listing of EEG interpretation data will be provided.

Change #8

9.2.1 Definition of treatment-emergent adverse events

AEs will be classified as either pre-study or treatment-emergent. Pre-study AEs are defined as AEs which had onset prior to the date of the first dose of BRV in EP0085 study.

…

Has been changed to:

9.2.1 Definition of treatment-emergent adverse events

AEs will be classified as either pre-treatment or treatment-emergent. Pre-treatment AEs are defined as AEs which had onset prior to the date of the first dose of BRV in EP0085 study.

…

Change #9

9.2.2 Summaries of TEAEs

Pre-study AEs will be provided in a subject data listing; no summary of pre-treatment AEs are planned. Summaries will be for TEAEs and will be provided overall by combining Evaluation Period, Down-Titration Period, and Study Drug-Free Period unless otherwise indicated.

…

Has been changed to:

9.2.2 Summaries of TEAEs

Pre-treatment AEs will be provided in a subject data listing; no summary of pre-treatment AEs are planned. Summaries will be for TEAEs and will be provided overall by combining Evaluation Period, Down-Titration Period, and Study Drug-Free Period unless otherwise indicated.

…

Change #10

9.3.4 Electrocardiograms (ECG)

…

A listing of subjects will be provided, in which details of abnormality and ECG reader (investigator or cardiologist) will be included. Subjects with QTc results > 500 msec or QTc change from Baseline > 60 msec will be flagged.

Has been changed to:

9.3.4 Electrocardiograms (ECG)

…

A listing of subjects will be provided, in which details of abnormality and ECG reader (investigator or cardiologist) will be included. Subjects with QTc results >= 500 msec or QTc change from Baseline >= 60 msec will be flagged.

13.4 Amendment 4

Rationale for the amendment

The main purpose of this amendment are

(1) To align the SAP with the protocol amendment 4.1. This Japan-specific protocol amendment is to update the terminology "clinical study" to "postmarketing clinical study" and related text that describes the continuing of EP0085 in Japan after the date of approval in Japan.
(2) To add time to BRV discontinuation analyses

Modifications and changes

Specific changes

Change #1

1 INTRODUCTION

…The SAP is based on the following study document: Protocol Amendment 4 and Case Report Form (CRF) version 8.0.

Has been changed to:

1 INTRODUCTION

…The SAP is based on the following study document: Protocol Amendment 4.1 and Case Report Form (CRF) version 8.0.

Change #2

The following new paragraph is added to section 2.3 Study design and conduct:

Subjects who will be converted to the commercial BRV product will complete an End of Study Visit without entering the Down-Titration Period or the 2-week Study Drug-Free Period and will not complete an FV.

Change #3

Section 2.3 Study design and conduct

…

In Japan, EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

Has been changed to:

…

In Japan, EP0085 will continue as a postmarketing clinical study (Phase 4) after the date of approval of BRV for the partial seizure indication ~~until approximately 6 months after the date of BRV approval for the partial seizure indication~~.

Change #4

The following new section is added for time to BRV discontinuation analysis:

5.4 Time to BRV discontinuation

As an additional assessment, the time to BRV discontinuation will be evaluated for both the overall study population and the Japanese subpopulation.

The time to BRV discontinuation will be calculated as follows:

(Date of last dose of BRV – date of first dose of BRV +1) / 30 (in month)

The time to BRV discontinuation will be analyzed using Kaplan-Meier method. The median time, 25% percentile, and 75% percentile of time to BRV discontinuation will be calculated based on SS. Additionally, the cumulative number of events, number at risk, and survival estimate at month 12, 24, 36, 48, 60, 72, 84 and 96 will be provided.

Subjects who discontinued BRV for any reason will be considered as an event. All other subjects will be censored at the date of the last dose of BRV.

In addition to analyzing BRV discontinuation due to any reason, the time to BRV discontinuation will be separately analyzed for the following specific reasons:

- Due to TEAE
- Due to lack of efficacy
- Due to lack of efficacy or TEAE

For each of the BRV discontinuation reason, a summary table will be provided by study group. Additionally, a Kaplan-Meier figure will be provided combing all discontinuation reasons and presented, by study group.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

Name: ep0085-sap-amend-4

Version: 1.0

Document Number: CLIN-000272131

Title: ep0085-sap-amend-4

Approved Date: 05 Feb 2025

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-Feb-2025 02:43:17 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-Feb-2025 14:37:48 GMT+0000