STATISTICAL ANALYSIS PLAN

Study: EP0077

Product: Brivaracetam

BASE: Brivaracetam And Seizure reduction in Epilepsy
A 12-MONTH NONINTERVENTIONAL, POSTMARKETING, MULTICENTER STUDY TO EVALUATE THE EFFECTIVENESS OF BRIVIACT® (BRIVARACETAM) AS ADJUNCTIVE THERAPY IN PATIENTS WITH EPILEPSY WITH PARTIAL-ONSET SEIZURES IN DAILY CLINICAL PRACTICE

SAP/Amendment Number	Date
Final SAP	04 Mar 2016
Amendment 1	13 Apr 2017
Amendment 2	26 Feb 2018
Amendment 3	07 Nov 2019
Amendment 4	09 Jun 2020

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AED	antiepileptic drugs
BID	“bis in die”/twice daily
BRV	brivaracetam
CGIC	Clinical Global Impression of Change
CI	confidence interval
CRO	contract research organization
CSR	Clinical Study Report
CRF	Case Report form
DDD	Defined Daily Dose
DEM	data evaluation meeting
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NIS	noninterventional study
OSR	Other safety relevant
PGIC	Patient's Global Impression of Change
POS	partial-onset seizure
PT	Preferred Term
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Inventory-Form 31

SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedures
SS	Safety Set
SmPC	summary of product characteristics
TFLs	tables, figures and listings
VNS	vagus nerve stimulation
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of data collected in EP0077. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity with, the Final Protocol Amendment 1, dated 25-Oct-2018.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly.

The content of this SAP is compatible with the International Conference on Harmonization (ICH)/ Food and Drug Administration (FDA) E9 Guidance documents (ICH E9, 1998).

UCB is the Sponsor and PRA Health Sciences is the contract research organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objective(s)

2.1.1 Primary objective(s)

The primary study objective is to evaluate the effectiveness of brivaracetam (BRV) in patients with epilepsy with partial-onset seizures (POS) with or without secondary generalization in daily clinical practice.

2.1.2 Secondary objective(s)

The secondary objective is to evaluate seizure control with BRV treatment.

2.2 Study variables

2.2.1 Primary variable

The primary variable is the BRV retention at 12 months (end of Observation Period).

Note: This variable is used as a measure of effectiveness.

2.2.2 Secondary variables

The following secondary variables will be measured:

- BRV retention at 3 months
- BRV retention at 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 3 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 12 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to end of Observation Period
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 3 months

- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 6 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 12 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to end of Observation Period
- Response based on percent reduction in POS (seizures per 28 days) at 3 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at 6 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at 12 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at end of Observation Period (response is a reduction of ≥50%)
- Seizure freedom at 3 months
- Seizure freedom at 6 months
- Seizure freedom at 12 months
- Seizure freedom at end of Observation Period
- Time to first seizure after first dose of BRV

2.2.3 Other variables

The following other variables will be measured:

- Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) total and subscale scores at 3, 6, and 12 months and change in QOLIE-31-P scores from Baseline to 3, 6, and 12 months and end of Observation Period
- Presence of clinically meaningful change from Baseline to 3, 6 and 12 months and end of Observation Period in QOLIE-31-P
- EpiTrack® performance at 6 and 12 months
- EpiTrack change category from Baseline to 6 and 12 months and from 6 months to 12 months
- EpiTrack total score at 6 and 12 months and change from Baseline to 6 and 12 months
- EpiTrack total and individual subtest scores at 12 months and change in EpiTrack scores from Baseline to 12 months
- Clinical Global Impression of Change (CGIC) rating at 3, 6, and 12 months and end of Observation Period
- Patient's Global Impression of Change (PGIC) rating at 3, 6, and 12 months and end of Observation Period

- Change in drug load (ie, number of products, daily dose per given product, ratio of dose and Defined Daily Dose [DDD, http://www.whocc.no/atc_ddd_index/], frequency, drug class) of antiepileptic drugs (AEDs) from Baseline to 12 months and end of Observation Period

2.2.4 Tolerability and safety variables

The following tolerability and safety variables will be analyzed:

- Time to discontinuation of BRV due to adverse drug reactions (ADRs)
- Incidence of treatment-emergent AEs and ADRs
- Incidence of serious treatment-emergent AEs and ADRs
- Incidence of ADRs leading to discontinuation of BRV

2.3 Study design and conduct

EP0077 is a postmarketing, multinational, multicenter, prospective noninterventional study (NIS) conducted at approximately 100 sites in approximately 10 European countries, with a 12-month Observation Period. Brivaracetam will be prescribed according to normal clinical practice and in accordance with the current summary of product characteristics (SmPC) in Europe for BRV. It is planned to include 530 patients in the study.

The patients will be followed as per current clinical practice. No additional clinical diagnostic or monitoring procedures will be applied. The use of an epilepsy/seizure diary, as standard clinical practice, is a requirement to enter the study. The selected questionnaires will be used if part of the standard clinical practice at the sites for the management of patients with epilepsy. The choice of medical treatment is made independently by the treating physician in the regular course of practice and is not influenced by the NIS protocol.

The clinical evaluation of patients with epilepsy will be performed by the treating physician following routine clinical practice. All visits and assessments will be scheduled and conducted per routine clinical practice. It is anticipated that each patient will have approximately 4 visits during their participation in this study. These visits will consist of:

- Visit 1, Baseline, Day 1: represents the first day of BRV treatment
- Visit 2, approximately 3 months after Baseline
- Visit 3, approximately 6 months after Baseline
- Visit 4, approximately 12 months after Baseline or end of Observation Period

2.4 Determination of sample size

Initially, a sample size of 430 patients was chosen for this study in order to obtain 385 patients in the Full Analysis Set (FAS), which allows for approximately 10% of patients to not be included.

When the sample size is 385, a 2-sided 95% confidence interval (CI) for a single proportion using the large sample normal approximation will extend 0.05 from the observed proportion for an expected proportion of 0.50. As an example, given an observed retention rate of 50%, a sample size of 385 patients would give a 2-sided 95% CI of 45% to 55% based on the large sample normal approximation to the binomial distribution.

However, since the first 100 patients were all enrolled at sites in Germany in early 2016 and the enrollment in that country was closed, it was believed that ongoing enrollment in other countries would be following different best practices in BRV usage, which could lead to wide variation in this NIS. For this reason, 100 additional patients are planned to be enrolled to obtain 385 patients in the FAS at non-German sites.

It is, therefore, planned to have 530 patients, and withdrawals will not be replaced.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All analysis will be performed using SAS® (Statistical Analysis System) version 9.3, or higher (SAS Institute, Cary, NC, USA).

All variables will be summarized using descriptive statistics; there will be no inferential analyses. For continuous variables, summary statistics will include number of patients with available observations (n), mean, standard deviation (SD), minimum, median and maximum. Where applicable, the 25% quartile, 75% quartile and interquartile range will also be presented. In general, the mean, SD, median, quartiles and range will be displayed to 1 more decimal place than collected in the source data. Minimum and maximum, will be displayed to the same number of decimals used for the source data.

Categorical variables will be summarized using frequencies and percentages. If there are no patients in a specific Case Report form (CRF) category or programmed set of categories, then that row will be retained and 0 presented in the table. In general, if there are patients with missing data, a missing row will be added and percentages will be based on the number of patients in the analysis set (N). 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%.

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

3.2 General study level definitions

3.2.1 Relative day

The relative day of a given date "D" will be calculated as follows:

- For days prior to the first BRV administration:
  D – date of first BRV administration
- For days on or after date of first BRV administration and prior to or on the day of last BRV administration:
  D – date of first BRV administration + 1
- For days after the last BRV administration:
  D – date of last BRV administration
  A "+" will be shown at the start to denote posttreatment days

Hence, the first day of BRV administration is Day 1, the day before the first BRV administration is Day -1, and the day after the last dose of BRV is Day +1. Relative day will not be calculated for partial dates.

3.2.2 Visit 4, Month 12/Withdrawal Visit

Patients with early study termination (ie, those who complete the Study Termination [Dropout] CRF page), will have their Visit 4 (Month 12/Withdrawal) visits prior to the preferred visit window for Month 12 of greater than or equal to 330 days after date of first BRV administration. Patients completing the study (ie, those who complete the Study Termination NIS [Completed Subject] CRF form), will have their Visit 4 (Month 12/Withdrawal) visits within the preferred visit window for Month 12 of greater than or equal to 330 days after date of first BRV administration. Therefore, Visit 4 will be analyzed as follows depending on the objective and variable being analyzed:

- Visit 4 (Month 12): Including only patients who are study completers with a Visit 4 within the preferred visit window for Month 12 of greater than or equal to 330 days after the date of first BRV administration.
- Visit 4 (Month 12/Withdrawal): Including all data recorded at Visit 4 (ie, completers or patients who withdraw early)

In addition, Visit 4 (Month 12/Withdrawal) visits that correspond to scheduled visits will be included in the counts for the scheduled visits to which they correspond. To be classed as corresponding to the scheduled visit, the withdrawal visit must fall into the windows provided below and the patient have no scheduled visit already available. Only the variables below will have the mapping of withdrawal visits applied.

Variables	Visit 2, Month 3	Visit 3, Month 6
Disposition (Patients attending each visit)	30-135	136-329
Seizure Frequency	30-135	136-329
QOLIE	30-135	136-329
CGIC/PGIC	30-135	136-329
EpiTrack	No mapping as no scheduled visit	150-210

3.2.3 Date of first administration of BRV

Date of first administration will be defined as the date of first BRV administration on the "First Administration of Drug" CRF page. If there is no data related to BRV medication (i.e. on the "First Administration of Drug" CRF page, “Brivaracetam Medication” CRF page, or study termination pages) available, then it is assumed the patient did not take BRV, and date of first administration will not be imputed. If the date of first BRV administration is missing on the

"First Administration of Drug" CRF page, then the first non-missing date on the “Brivaracetam Medication” CRF page will be used as the first BRV administration date. In case of a partial date, then use the imputation of partial first BRV administration date rules as described in Section 4.2.2. Otherwise the Visit 1 date will be used. This means that for example if a patient has a non-missing date for “Date of last administration of medication (Brivaracetam) while in the study” on the study termination page, no dates on the "First Administration of Drug" CRF page, “Brivaracetam Medication” CRF page then the Visit 1 date will be used.

3.2.4 Date of last administration of BRV

Date of last administration of BRV will be defined as last administration of BRV while in the study as recorded in the Study Termination (Dropout) or (Completed Subject) CRF pages. If the date is partial, then use the imputation of partial end dates rules as described in Section 4.2.2.

For the snapshot analyses described in Section 4.3, patients ongoing in the study will not yet have a date of last administration of BRV recorded. For these patients the date of last administration of BRV will be imputed using the date of the data cut off so that an estimate of the exposure to date can be calculated.

For patients who have completed or withdrawn from the study, if the date of last administration is missing, then the last end date from the BRV Medication CRF page (applying the imputation of partial end dates rules as required) will be used. If that date is also missing then the date of first BRV administration as described in Section 3.2.3 will be used. If all of the above are missing, then it is assumed the patient did not take BRV.

3.2.5 VNS Use

Patients will be considered to have VNS use if the answer to the CRF question “Has a VNS magnet been used?” is equal to “Yes”.

3.3 Definition of Baseline values

In this NIS, Baseline is defined as the data collected at Visit 1. For prior and concomitant medications and for AED drug load, Baseline is defined as first BRV administration. For seizure frequency variables, Baseline is defined in Section 8.2.2.1.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary effectiveness or key safety/tolerability for an individual patient. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific documents. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. In addition, prior to database lock, all important protocol deviations will be reviewed during the data evaluation meeting (DEM), in order to confirm exclusion from the study analysis sets defined in Section 3.5.

3.5 Analysis sets

The All Subjects Documented set is defined as all patients included in the study with valid data consent and for whom at least Visit 1 (Baseline) is documented. The All Subjects Documented set will be used for patient disposition and patient data listings only.

The Safety Set (SS) is defined as all patients included in the All Subjects Documented set for whom it cannot be excluded that they received treatment with BRV at least once in the study. Evidence of BRV dosing will be determined based on patients meeting 1 or more of the following criteria:

- At least 1 entry with a total daily dose >0 recorded in the BRV Medication (NIS) CRF page
- A present date of first BRV administration during observational study, recorded in the First Administration of BRV CRF page
- A present date of last BRV administration while in the study, recorded in the Study Termination (Dropout) or Study Termination (Completed Subject) CRF pages

The SS will be used for the summary of the safety data, Baseline characteristics of the patients, and important protocol deviations.

The Full Analysis Set (FAS) is defined as all patients in the SS who did not receive BRV before entering this NIS. Any patients with a documented protocol violation of Selection Criterion #1 will be considered to have been treated with BRV prior to inclusion in this NIS and will be excluded from the FAS. The FAS will be used for the analysis of BRV retention (ie, the primary variable), the secondary variables, and other variables.

The modified FAS is defined as all patients in the FAS who are treated according to the approved SmPC during their Observation Period, representing the on-label use of BRV. Compliance with the approved SmPC is defined as follows:

- Patient has POS with or without secondary generalization at Baseline (ie, patient does not have a protocol violation of Selection Criterion #5)
- All documented BRV doses were less than or equal to the maximum approved dose of 200mg/day
- BRV doses were greater than or equal to the minimum approved dose of 50mg/day (with the exception of down-titrating). Per the SmPC, a down-titration of BRV is allowed to 20mg/day, hence any patients receiving BRV doses lower than 50mg/day from day 2 onwards will be reviewed during the DEM to determine whether they are taking BRV per SmPC.
- BRV doses were administered in 2 equally divided doses (BID). According to when the first dose or last dose is administered, other administration schemes can occur. Hence any patients receiving BRV not divided into 2 equally doses will be reviewed during the DEM to determine whether they are taking BRV per SmPC.
- BRV is administered as an adjuvant therapy, defined as
  - patient receiving at least 1 concomitant AED at Baseline and at each post-Baseline documented visit.
  - patient does not have a protocol violation of Selection Criterion # 6

Modified FAS listings to investigate compliance with the approved SmPC will be created and reviewed at the DEM prior to database lock in order to determine which patients will be included in the modified FAS. If the number of patients in the modified FAS is sufficiently different to

that in the SS, then key demographic, effectiveness and safety tables will be repeated on the modified FAS.

3.6 Treatment assignment and treatment groups

Brivaracetam will be prescribed according to normal clinical practice for all patients in the study. Therefore, there is only 1 treatment group. For this group the label "BRV" is used.

3.7 Center pooling strategy

No pooling of centers is planned for this study as data will be summarized altogether.

3.8 Coding dictionaries

Adverse drug reactions will be coded using version 23.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the September 2017 version of World Health Organization Drug Dictionary (WHODD). Medical history is not being collected for this study and concomitant medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

A summary of the change from Baseline to 6 months in individual subtest scores was added to be consistent with the analysis of the EpiTrack total score.

According to the protocol seizure freedom at the end of the Observation Period should be presented. However seizure freedom at the end of the Observation Period will not be presented.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

There will be no adjustments for covariates.

4.2 Handling of dropouts or missing data

Missing data will not be imputed with the exceptions described below.

4.2.1 Seizure diary

Seizure data will be recorded at each visit as described in Section 8.2.2.1.

The treating physician will use the patient diaries to calculate the number of seizures since the previous visit and will enter this information into the CRF. Hence, if a patient misses a visit, as long as they have diaries available when they attend the next visit, then the seizure information can still be utilized.

4.2.2 Times and Dates

Partial dates may be imputed for statistical analyses for specific outcomes according to the following rules. There will be no imputation of missing times. In general, imputed dates will not be shown in listings with the exception of showing imputed dates alongside partial dates for key derivations.

Imputation of partial first BRV administration date:

- If the day of first BRV administration is missing and the month and year are the same as the month and year of Visit 1 then the date of Visit 1 will be imputed as the date of first BRV administration. Otherwise impute 1st of the month.
- If the day and the month of first BRV administration are missing then no imputation of the partial date will be done.

Imputation of partial start dates:

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

Imputation of partial end dates:

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

The imputation rules should not create an inconsistency in the data.

4.3 Interim analyses and data monitoring

No formal interim analyses are planned; however, 3 nonformal interim analyses (snapshot analyses) were performed in order to assess early treatment effectiveness, as follows:

- A first snapshot analysis was to be performed with a data cut-off date approximately at the end of 2016 or when 80 patients have completed Visit 2 (Month 3), whichever occurs first. The snapshot was taken on 05 Oct 2016. All patients with available data in the database were included in the analyses. A subset of the end of study TFLs were produced.
- A second snapshot analysis was to be performed with a data cut-off date approximately at the end of 2017, depending on recruitment status. If the recruitment schedule would have resulted in there not being enough additional data from the previous snapshot then the snapshot cut-off date could have been delayed to ensure approximately 200 patients had Visit 2 (Month 3). The snapshot was taken on 13 Apr 2018. All TFLs identified in the SAP and Mock TFL shells at the time of the snapshot were delivered including all visits available in the database at the time of the snapshot cut off.
- A third snapshot analysis was performed with a data cut-off date on 28 Nov 2019. All TFLs identified in the SAP amendment 3 and Mock TFL shells were delivered including all visits in the database at the time of the snapshot cut off.

As data is entered in an ongoing way throughout the study and cleaning is ongoing, data discrepancies in the snapshot analyses are possible. Any data discrepancies observed in the database at the time of the snapshot analyses were discussed and their impact on the analysis documented.

4.4 Multicenter studies

The data from different centers will be summarized together.

4.5 Multiple comparisons/multiplicity

No adjustments for multiplicity will be made as the statistical analyses will be exploratory in nature.

4.6 Use of subsets of subjects

All effectiveness analysis will be performed on the FAS and the modified FAS to estimate the effectiveness for patients using BRV per the approved SmPC.

In addition, the responder analysis and the seizure freedom analysis will be repeated on the FAS and modified FAS for:

- patients who completed the study
- patients who discontinued the study due to a lack of efficacy

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

- Age at Visit 1 (<65 and ≥65 years).
- Time since first diagnosis of epilepsy (0-<1 years, 1-<5 years, 5-10 years, >10 years): Defined in Section 6.2
- Number of AEDs at study entry (0, 1, 2, 3 and >3 AEDs) : Defined in Section 6.4
- Number of Historical AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- Historical Levetiracetam (LEV) use (Yes, No): Defined in Section 6.4
- Number of Lifetime AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- 28-day Baseline all seizures frequency (≤5, >5-10, >10): Defined in Section 8.2.2.1

The number of patients in the subgroup categories listed above will be examined at the DEM meeting to ensure sufficient patients exist in each category for statistical analysis of the primary and secondary variables by subgroup to offer meaningful analyses. For example, if it is deemed that there are an insufficient number of patients in the ≥65 years age at Visit 1 category, then the age at Visit 1 categories may be amended to use <60 and ≥60 years instead.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The following tables will be produced on the All Subjects Documented set:

- Disposition of All Subjects Documented. For all study sites and by study site, this table will show the date of the first patient in/last patient out and the number of patients in the All Subjects Documented set, FAS, SS and modified FAS.
- Disposition of Analysis sets to include the number and percentage of patients in the All Subjects Documented set, FAS, SS and modified FAS
- Disposition and Discontinuation Reasons including:
  - Number and percentage of patients completing or prematurely discontinuing the study with discontinuation reason (as recorded in the Study Termination NIS (Dropout) and Study Termination NIS (Completed Subject) CRF pages)
  - Number and percentage of patients continuing or discontinuing BRV after study participation in this NIS with discontinuation reason (as recorded in the Post-Study Treatment Continuation and Medication Discontinuation CRF pages)
- Number and percentage of patients attending each scheduled visit (including mapping of withdrawal visits as described in Section 3.2.2)

In addition to a study eligibility criteria text listing, the following by-patient listings on the All Subjects Documented set will be produced:

- Patients who did not meet study eligibility criteria
- Patient disposition (including first and last BRV dose, completion and early discontinuation information, primary reason for discontinuation, whether the patient is prescribed BRV after exiting the study and the main reason for BRV discontinuation)
- Patient discontinuation (only including patients who discontinue)
- Patient analysis sets
- Patients excluded from analysis sets with reason for exclusion
- Visit dates

5.2 Protocol deviations

Important protocol deviations will be identified at the DEMs as described in Section 3.4. The number and percentage of patients in the All Subjects Documented set with at least 1 important protocol deviation and with at least 1 important protocol deviation by deviation type will be summarized. This will include a summary of the number of patients not meeting the selection criteria. The denominator for percentages will be the number of patients in the All Subjects Documented set. A by-patient listing will be presented for all patients in the All Subjects Documented set, and will include the deviation type and description.

6 DEMOGRAPHICS AND OTHER BASELINE DISEASE CHARACTERISTICS

All demography, Baseline disease characteristics, and historical and concomitant medication summaries will be presented on the SS and modified FAS, except for subgroup analyses that will only be presented on the SS. Demography will be also presented on the All Subjects Documented set. Listings of all data will be presented on the All Subjects Documented set.

6.1 Demographics

The following patient demographics will be summarized.

- Age at Visit 1 (years) – Age will be taken from the CRF and summarized as a continuous variable in addition to the following categories:
  - <65 and ≥65
  - <18 years, ≥18 - <65 years, and ≥65 years (in addition, the ≥65 years category will also be broken down into ≥65 - ≤75, >75 - ≤85, and >85)
  - ≤18 years, >18 - <65 years, and ≥65 years
- Gender (male, female)

A by-patient listing of the date of birth (year only), age, and gender will be provided. If required, the listing will be repeated for patients aged <18 years only.

6.2 Other Baseline disease characteristics

The following Baseline disease characteristics will be summarized:

- History of Epilepsy
  - Time since first diagnosis of epilepsy (years)
    (Date of Visit 1 – Date of first diagnosis of epilepsy) / 365.25
    Note that as the day of first diagnosis is not collected in the CRF it will be imputed per the rules outlined in Section 4.2.2. If the time since first diagnosis is greater than the patient's age due to the application of imputation rules, then time since first diagnosis will be set to equal the patient's age. If the time since first diagnosis is less than or equal to 0 due to the imputation rules, then time since first diagnosis will be set to 0.
  - Time since first diagnosis of epilepsy (0-<1 year, 1-<5 years, 5-10 years, and >10 years)
  - Age at time of first diagnosis of epilepsy (years)
    Age – Time since first diagnosis of epilepsy
  - Percent of life with epilepsy
    100 x Time since first diagnosis of epilepsy (years) / Age
  - Reason for initiation of BRV (Behavioral side effects to current AED, Other intolerance to current AED, Lack of efficacy of current treatment, Administer therapeutic dose without titration, or Other): as recorded in the Initiation of Medication CRF form
- Baseline seizure frequency as described in Section 8.2.2.1 summarized as a continuous variable and in the following categories (≤5, >5-10, and >10 seizures per 28-days)

  - 28-day Baseline all seizure frequency
  - 28-day Baseline POS frequency
  - 28-day Baseline POS with secondary generalization frequency

- Epilepsy etiology and seizure classification
  - Whether the etiology of epilepsy is known and the type of etiology as recorded in the Etiology of Epilepsy CRF form
  - Seizure history profile based on the 1981 International League Against Epilepsy (ILAE) Classification. Any POS (I) and each seizure sub type (IA [also broken down into IA1, IA2, IA3, IA4], IB and IC) as recorded in the ILAE Seizure Classification History CRF page

The following by-patient listings will be provided

- History and etiology of epilepsy (including time to first diagnosis, age at first diagnosis, percent of life with epilepsy, etiology, ILAE Seizure classification and reason for BRV initiation)
- Baseline seizure count (including number of all seizures, POS and POS with secondary generalization seizures)

6.3 Medical history and concomitant diseases

Medical history (with the exception of that related to epilepsy) and concomitant diseases are not collected in this study.

Concomitant medical procedures will be listed on the All Subjects Documented set including the procedure, detail of what the procedure is primarily related to, and the date of the procedure.

6.4 Prior and concomitant medications

Medications will be reviewed during the DEM to ensure correct classification. In addition, historical and concomitant medications will be reviewed to ensure documentation in the correct CRF pages. Historical medications are defined as medications discontinued prior to the date of first BRV administration. Medications at study entry are defined as those being taken on the same day as first BRV administration. Concomitant medications are medications taken at least 1 day in common with the study medication dosing period. In other words, those that started on or prior to the date of first BRV administration, and have an end date on or after the date of first BRV administration or are ongoing; or those starting after the first BRV administration and on or before last BRV administration.

Non-AED historical medications, those stopped before the date of first BRV administration, should not be collected in the CRF.

As there are snapshot analyses throughout the study and data entry is ongoing, any non-coded terms at the time of reporting will report the WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3] and PT as UNCODED in the tables and listings.

The number and percentage of patients with each of the following medication types will be summarized overall and by WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3] and PT.

- Number and percentage of patients with AED concomitant medications (including LEV)
- Number and percentage of patients with non-AED concomitant medications

Where necessary, PTs may be collapsed into AED PT categories for study reporting and where applied this will be added as a footnote on the output. In addition, LEV use will be combined with other AED medications and reported in the table of AED concomitant medications.

Patients documented as having used a vagus nerve stimulation (VNS) magnet will be considered as having active use on the date of first BRV administration and during the study. Hence, VNS use is counted as an AED for AEDs taken at study entry. As historical AEDs are defined as medications discontinued prior to the date of first BRV administration, VNS use at study entry will not be counted as a historical AED. Lifetime AEDs are defined as a sum of the historical AEDs and AEDs taken at study entry. As LEV can be included in both historical AEDs and AEDs at study entry, it will only be counted once in the calculation of Lifetime AEDs.

VNS use, number of historical AEDs, number of AEDs at study entry, Lifetime AEDs and LEV use will be summarized as follows:

- Number of patients with/without a VNS magnet
- Number of patients with historical and LEV use at study entry
- Number of historical AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)
- Number of AEDs at study entry, presented using summary statistics and the following categories (0, 1, 2, 3 and >3)
- Number of Lifetime AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)

The summaries above will be repeated for the subgroups of patients with and without VNS use, and with and without historical LEV.

The following listings will be provided:

- Concomitant medications glossary. To include the WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3], PT, and Reported Term (Medication)
- By-patient listings of the WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3], PT, reported term (medication), dose, unit, frequency, formulation, indication, start and end dates/ongoing (and including the reason for discontinuation for LEV if applicable) will be presented for the following medications for the All Subjects Documented set
  - Concomitant AED medications (including LEV use)
  - Concomitant non-AED medications
  - Historical LEV use (including the reason for discontinuation)

- By-patient listing of VNS use, historical AEDs, historical LEV use, LEV use at Study Entry, and the number of historical and AEDs at Study Entry.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance with BRV study medication will not be assessed in this NIS.

8 EFFECTIVENESS ANALYSIS

All effectiveness analyses will be performed on the FAS and the modified FAS, except subgroup analyses that will only be performed on the FAS.

8.1 Statistical analysis of the primary variable

8.1.1 Retention at 12 months

Patients who remain in the study and are on BRV treatment 1 year after their start of BRV will be classed as having 12 months of treatment retention. More specifically, a patient will be categorized as having 12 months BRV retention if they do not meet either of the following criteria:

- Date of study termination < date of first BRV administration + 330 days
- Date of last administration of BRV while in the study < date of first BRV administration + 330 days

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 12 months BRV retention. Date of last administration of BRV will be derived as described in Section 3.2.4. 330 days is used to represent 1 year of treatment in accordance with the visit window instructions given to sites (i.e., that the 12 month visit should not be prior to 330 days). This is to prevent classing patients as not having BRV retention when in fact they completed the study within 30 days of the target 360 days.

The number and percentage of patients achieving 12 months retention will be presented on the FAS along with a 2-sided exact (Clopper-Pearson) 95% CI for the percentage.

A by-patient listing of patient retention data including dates of first and last BRV administration, date of study termination, time to discontinuation of BRV or study termination, visit window target dates, and retention at 3, 6 (as described in Section 8.2.1), and 12 months will be listed on the All Subjects Documented set.

8.1.2 Sensitivity analysis of the primary variable retention at 12 months

The 12 month retention analysis described in Section 8.1.1 will be repeated on the modified FAS as a sensitivity analysis to represent the retention of patients who take BRV per the SmPC.

In addition, a Kaplan-Meier analysis of time to discontinuation of BRV or study termination will be provided on the FAS and the modified FAS. Time to discontinuation of BRV or study termination will be calculated as:

Minimum of (Date of last administration of BRV while in the study, Date of study termination) – date of first BRV administration + 1

A patient will be considered as having an event if the patient discontinues from the study (Study Termination [Dropout] CRF page completed) or if the patient is not prescribed Brivaracetam

after exiting the study (ie, answer to the CRF question "Will the subject be prescribed Brivaracetam after exiting the EP0077 study?" is "No"). All other patients will be considered as not having an event and will be censored at the date of study termination. For snapshot analyses, patients ongoing in the study will be censored at the date of data cut off.

The median time to event (days) will be presented along with the 25% and 75% quartiles and 95% CIs. In addition, the cumulative number of events, number at risk and survival estimate at monthly intervals will be provided. The Kaplan-Meier plot and raw statistical procedure output will be produced for the Kaplan-Meier analysis.

8.1.3 Subgroup analysis of the primary variable retention at 12 months

The analysis described in Section 8.1.1 will be repeated for each of the subgroups described in Section 4.8.

8.2 Statistical analysis of the secondary variables

8.2.1 Retention at 3 and 6 months

Similar to the primary endpoint, patients will be classed as having 3 months BRV retention if they do not meet either of the following criteria:

- Date of study termination < date of first BRV administration + 90 days
- Date of last administration of BRV while in the study < date of first BRV administration + 90 days

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 3 months BRV retention. 90 days is selected because at least 3 months BRV retention is required, hence a patient who attends a month 3 visit early and terminates BRV prior to Day 90, would not be classed as having 3 months retention.

Patients will be classed as having 6 months BRV retention if they do not meet either of the following criteria:

- Date of study termination < date of first BRV administration + 180 days
- Date of last administration of BRV while in the study < date of first BRV administration + 180 days

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 6 months BRV retention. 180 days is selected because at least 6 months BRV retention is required, hence a patient who attends a month 6 visit early and terminates BRV prior to Day 180 would not be classed as having 6 months retention.

BRV Retention at 3 and 6 months will be summarized using the methods described in Section 8.1 for the FAS and the modified FAS. BRV Retention at 3 and 6 months will be listed as described in Section 8.1.1.

8.2.2 Seizure frequency related variables

8.2.2.1 Initial processing of diary data

The number of POS since the last visit will be reported at each visit and Month 12/ Withdrawal. The 28-day post-Baseline seizure frequency for POS will be calculated as:

$$\frac{\text{Number of POS recorded at visit}}{\text{(Date of visit – Date of previous visit)}} \times 28$$

Partial-onset seizures frequency will only be calculated at visits attended and with seizure data recorded. For seizure frequency summaries, data recorded at Visit 4 (Month 12/Withdrawal) visit will be mapped to the appropriate scheduled visits as described in Section 3.2.2. No mapping will be performed for Seizure freedom as the derivation is date based rather than visit based.

Twenty eight-day Baseline POS frequency (28-day Baseline) will be calculated using the Historical Seizure Count CRF page, as the number of POS recorded during the 3 months prior to first BRV administration / 3. For all seizures and POS with secondary generalization, the 28-day Baseline will be calculated using the same method of dividing the number recorded during the 3 months prior to first BRV administration by 3.

If Visit 4 data are missing, then the Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) seizure rates will be missing. Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) will be derived according to Section 3.2.2.

8.2.2.2 Derivation of seizure frequency related variables

The following variables will be defined for each visit and Month 12 /Withdrawal using the 28-day Baseline and 28-day post-Baseline seizure frequency variables described in Section 8.2.2.1.

- Absolute reduction in POS frequency defined as:
  28-day Baseline – 28-day post-Baseline seizure frequency
- Percent reduction in POS frequency defined as:
  $$\frac{\text{28-day Baseline – 28-day post-Baseline seizure frequency}}{\text{28-day Baseline}} \times 100$$
- Patients with 0 POS at Baseline will be excluded from the analysis of percent reduction and response (≥50%).
- Response (Yes, No) where Yes is ≥ 50% reduction in POS frequency calculated as described above and No otherwise.
- Seizure freedom (Yes, No) will be defined using 2 methods as shown in Table 8–1. The first method considers patients who withdraw prior to their 1st seizure as Not seizure free. The 2nd is a less conservative method which considers patients who withdraw prior to their 1st seizure as missing. Visit 4 (Month 12/Withdrawal) will not be summarized for seizure freedom.

Table 8–1: Derivation of seizure freedom

Patient Classification at Visit (patients are assigned to the first category they fall into)	Seizure freedom – Discontinuations counted as not seizure free	Seizure freedom – Discontinuations counted as missing
0. Patients had a seizure before 1st BRV dose	Missing	Missing
1. Patient had a seizure on or after 1st BRV dose and on or before the visit date derived using the following conditions. First_seizure_date = Date of first seizure or if date of first seizure is missing but patient has seizures recorded at a visit, then assign first_seizure_date as the date of the visit prior to the earliest visit with seizures recorded a) Visit date present and First_seizure_date is on or after 1st BRV and on or before the Visit date b) Visit date is missing (either due to patient ongoing in study or visit missed) and First_seizure_date is on or after 1st BRV and on or before the visits target day [a])	No	No
2. Patient discontinued BRV or terminated the study prior to the visit's target day [a]	No	Missing
3. Patient had missing seizure data at the visit (or missed the visit) but had not discontinued BRV or terminated the study prior to the visit's target day [a] Note: If a patient is ongoing in the study and had not got to the visit yet, they are treated in the same way as having missed visit.	Missing	Missing
4. Patient met none of the above classifications and patient has the visit present	Yes	Yes

[a] The target day for each visit is: Visit 2 (Month 3) = Day 90, Visit 3 (Month 6) = Day 180, and Visit 4 (Month 12) = Day 330. For Month 12 assessments, seizure freedom will be analyzed for completers only. Therefore assign missing to all patients who withdraw for the Month 12 analyses.

8.2.2.3 Analysis of seizure frequency related variables

The following tables will be produced on the FAS and all tables except the by subgroup tables will be repeated on the modified FAS:

- Descriptive statistics of the POS frequency at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Descriptive statistics of the absolute reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)

- Descriptive statistics of the absolute reduction in POS frequency (seizures per 28 days) by subgroups described in Section 4.8, from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal).
- Descriptive statistics of the percent reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Number and percentage of responders (≥ 50% reduction) at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- A sensitivity analysis of the responder analysis will be performed on two subsets of the FAS and modified FAS as defined in Section 4.6 (patients who completed the study and patients who discontinued the study due to lack of efficacy).
- Number and percentage with seizure freedom (using the 2 methods described in Table 8–1) at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12)
- A sensitivity analysis of the seizure freedom analysis will be performed on two subsets of the FAS and modified FAS as defined in Section 4.6 (patients who completed the study and patients who discontinued the study due to lack of efficacy).
- Number and percentage with seizure freedom (using discontinuations counted as seizure freedom = no) by subgroups described in Section 4.8, at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12)

The following by-patient listings of seizure data will be produced on the All Subjects Documented set:

- Seizure Frequency by Type (including by visit data of number of All, POS, and POS with secondary generalization seizures (IC) at Baseline, since the last visit and adjusted for 28-day frequency. In addition, the number of days since last visit, number of days POS occurred since last visit, and the 28-day POS frequency absolute and percentage reduction from Baseline will be presented).
- Time to first seizure (as described in Section 8.2.3) and seizure freedom, including the date of first and last BRV administration, the date of study termination, the date of first seizure in the study, the time to first seizure, the visit window target dates, and seizure freedom at 3, 6, and 12 months (using the 2 methods described in Table 8–1).

8.2.3 Time to first seizure

The time to the first seizure (days) will be calculated as:

Date of first seizure in the trial – date of first BRV administration + 1

If the exact date of first seizure cannot be determined but the patient has had seizures recorded post Visit 1, then the patient will still be counted as having an event using a conservative approach as shown in Table 8–2.

For patients with no evidence of seizures, the following sequential approach will be taken which is further detailed in Table 8–2:

1. For patients attending a visit but with missing seizure data, they will be censored at the date of the last visit prior to the visit with the missing seizure information.
2. For patients discontinuing BRV study medication before experiencing their first seizure, they will be censored at the date of last administration of BRV while in the study.
3. For patients with no recorded seizures and still on BRV study medication, they will be censored at the date of last visit.

As the approach used is very conservative, if there are a lot of patients censored in the early visits due to missing data or with early events due to missing data, a sensitivity analysis may be performed.

Table 8–2: Derivation of time to first seizure

Missing date of first seizure but seizures recorded				No evidence of seizures on the study			
V2	**V3**	**V4**	**Date used**	**V2**	**V3**	**V4**	**Date used**
M	M	>0	E-V1/1BRV [a]	M	M	M	C-V1
M	>0	NA	E-V1/1BRV [a]	0	M	M	C-V2
>0	NA	NA	E-V1/1BRV	M	0	M	C-V1
0	>0	NA	E-V2	M	M	0	C-V1
0	0	>0	E-V3	0	0	M	C-V3
M	-	>0	E-V1/1BRV [a]	0	M	0	C-V2
0	-	>0	E-V2	M	0	0	C-V1
-	>0	NA	E-V1/1BRV [a]	0	0	0	C-V4
-	M	>0	E-V1/1BRV [a]	0	Disc BRV	NA	C- Last BRV
				M	Disc BRV	NA	C-V1

[a] The rationale behind using V1/1BRV in this scenario is based on it being unknown when exactly between V1 and V4 that the first seizure event occurred. V1/1BRV is more conservative and hence will be used, however a sensitivity analysis may be performed if there are a lot of patients with missing data.

Note: M=patient is missing seizure data at this visit but attended the visit, - = patient missed entire visit, NA=Visit is not applicable/not required to be considered in this scenario, V=Visit, C=Censor, E=Event, 1BRV= Date of first dose of BRV, Last BRV= date of last dose of BRV.

Note: V1/1BRV implies the date of the first dose of BRV should be used if it is later than V1 to avoid negative time to events and under-reporting of potential seizure events. For patients with no evidence of seizures on the study, negative censoring times are acceptable as it is equivalent to censoring the patient on Day 1.

The time to first seizure from the date of first dose of BRV will be analyzed using Kaplan-Meier methods, from which the median time to first seizure (and 95% CI) will be calculated, along with 25% and 75% quartiles (and 95% CI for the quartiles). In addition, the cumulative number of events, number at risk, and survival estimate at monthly intervals will be provided. The Kaplan-Meier plot and raw statistical procedure output will be produced for the Kaplan-Meier analysis. This will be performed on the FAS and the modified FAS.

8.3 Analysis of other variables

8.3.1 Patient Weighted Quality of Life in Epilepsy Inventory-form 31 (QOLIE-31-P)

The QOLIE-31-P includes 30 items grouped into 7 multi-item subscales (seizure worry [5 items], overall quality of life [2 items], emotional well-being [5 items], energy/fatigue [4 items], cognitive functioning [6 items], medication effects [3 items], and social function [5 items]) and a health status item. The QOLIE-31-P total score, subscale scores, and health status item score are calculated according to the scoring algorithm described below, with scores ranging from 0 to 100 and higher scores indicating better functioning.

8.3.1.1 Derivation of QOLIE-31-P scores

Subscale scores: as a first step to calculating the subscale scores, the individual responses for the 30 subscale items are rescaled to a 0 to 100 scale with higher scores reflecting better functioning; the rescaled values for each item are defined in Section 12.1 . Each subscale score is then calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Total score: total score is calculated as a weighted sum of the subscale scores based on the weighting in Section 12.1 . Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

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

The change from Baseline (CFB) at each Visit for the subscale scores, total score, and health status item will be calculated as:

Derived score at post-Baseline visit – Derived score at Visit 1 (Baseline)

A clinically meaningful change (CMC) in QOLIE-31-P from Baseline is defined based on the minimally important changes in Table 8–3; Borghs et al, 2012.

For each subscale and total score:

- Improvement is defined as: CFB ≥ CMC
- No change is defined as: - CMC < CFB < CMC
- Worsening is defined as: CFB ≤ - CMC

Table 8–3: QOLIE-31-P Clinically Meaningful Change Criteria	
Subscale Score	**Clinically Meaningful Change (CMC)**
Energy/Fatigue	5.25
Emotional Well-Being	4.76
Social Functioning	3.95
Cognitive Functioning	5.34
Medication Effects	5.00
Seizure Worry	7.42
Overall Quality of Life	6.42
Total Score	5.19

8.3.1.2 Analysis of QOLIE-31-P scores

All QOLIE-31-P analyses will be performed on the FAS and the modified FAS.

Descriptive statistics will be presented for QOLIE-31-P: 7 multi-item subscales, the health status item, and total score, and the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal). As described in Section 3.2.2, Visit 4 (Month 12/Withdrawal) visits will be mapped to the appropriate scheduled visit and Visit 4 (Month 12) will only include patients completing the study.

The number and percentage of patients with clinically meaningful changes in QOLIE-31-P total and subscale scores from Baseline (improvement, no change, or worsening) will be presented for Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal).

A question glossary and by-patient listings of QOLIE-31-P scores (including all items of the subscale scores, the total subscale scores, the total score, the health status item, changes from Baseline, and whether patients achieved a clinically meaningful change) will be provided for the All Subjects Documented set.

8.3.2 EpiTrack

All EpiTrack analyses will be performed on the FAS and the modified FAS. EpiTrack score after age correction will be referred to as "EpiTrack total score".

Descriptive statistics will be provided for the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests. Visit 4 (Month 12/Withdrawal) visits will be mapped to Visit 3 (Month 6) if they are within the windows described in Section 3.2.2. EpiTrack results by visit and the changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12) will also be displayed. The same age correction (age at Visit 1) will be applied at all visits even if a patient changes age category during the study. If any of the individual point scores are outside of the plausible range then they will be set to missing in the tables but will be listed in the listings. If a patient is missing any of the individual point scores or the individual point score is outside of the plausible range then the EpiTrack total score will be missing. Change from Baseline will be calculated as:

Post-Baseline score – Baseline score.

The number and percentage of patients in the following categories (calculated as described in Section 12.2) will be provided:

- Point score categories (rated 1-7 for Interference, Numbers, Numbers and letters, and Maze test; 2-7 for Verbal fluency and 3-7 for Inverted digit span)
- Cognitive performance categories (excellent, average, mildly impaired, or significantly impaired) at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 4 (Month 12)
- Significant change categories of cognitive function (improved, unchanged, or worsened) for:
  - Visit 3 (Month 6) compared to Visit 1 (Baseline)
  - Visit 4 (Month 12) compared to the Visit 1 (Baseline)
  - Visit 4 (Month 12) compared to Visit 3 (Month 6).

By-patient listings of 6 EpiTrack individual subtest scores, the change from Baseline for the 6 individual subtest scores, and the age correction, EpiTrack total score and change from Baseline, cognitive performance categories, and significant change evaluation will be provided for the All Subjects Documented set.

8.3.3 Clinical Global Impression of Change (CGIC) and Patient's Global Impression of Change (PGIC)

The CGIC describing the patients condition over the past 4 weeks compared to Baseline (as assessed by the treating physician) and the PGIC describing how the patient felt over the past 4-weeks compared to before they entered the study, will each be assessed at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12) according to 7 categories (1=Very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse).

For both scales (CGIC and PGIC) the above categories will be collapsed into Improvement, No change, and Worsening as follows:

- Improvement: category 1, 2, or 3
- No change: category 4
- Worsening: category 5, 6, or 7

All CGIC and PGIC analyses will be performed on the FAS and the modified FAS. The number and percentage of patients with each CGIC and PGIC rating and who had improved, had no change, or worsened at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) will be presented. Visit 4 (Month 12/Withdrawal) visits will be mapped as described in Section 3.2.2.

A by-patient listing of CGIC and PGIC including categories of improvement or worsening will be provided on the All Subjects Documented set.

8.3.4 Change in drug load of AEDs

Drug load of AEDs will be calculated at first BRV administration, Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal). Drug load of AEDs will include all concomitant AEDs and LEV (recorded separately in the CRF), in addition to BRV dosing.

Only AEDs (recorded as an AED, as LEV, or as BRV dosing) that are being taken on the date of the visit will be included in the calculations. Partial dates will be imputed as described in Section 4.2.2 to ensure the inclusion of any medications which have the potential to have been taken on the date of the visit.

Drug load per AED at the visit is calculated as: daily dose (mg) / DDD,
where DDD for each AED is defined in Section 12.3 and daily dose for each AED is calculated as follows:

1. Convert the dose per intake into mg using the unit recorded for each AED in the CRF (ie, 1g = 1000mg)
2. Using the frequency of dose recorded, multiply the dose per intake in mg by the values shown in Table 8–4.

Table 8–4: Daily dose calculation

Frequency	Description	Multiply dose per intake by:
QD	Once daily	1
BID	Twice daily	2
TID	3 times daily	3
QID	4 times daily	4
5XD	5 times daily	5
6XD	6 times daily	6
QOD	Every other day	1/2
QAM	Every morning	1
QPM	Every evening	1
QS	Every week	1/7
Q2S	Every 2 weeks	1/14
BIS	Twice per week	2/7
TIS	3 times per week	3/7
QM	Every month	1/28
BIM	Twice per month	2/28
TIM	3 times per month	3/28
Q2M	Every 2 months	1/56
Q3M	Every 3 months	1/84
PRN	As needed	Excluded from calculation

The drug load per AED at each visit will be added together to give a total AED drug load per visit. To avoid an underestimation of the drug load on the first and last visits (on which only 1 of the usual 2 doses may have been recorded), AED drug load at first BRV administration will be

calculated for the Day 2 for all patients and the last available record with morning and evening dosage will be used for the Visit 4 drug load analysis.

All drug load analyses will be performed on the FAS and the modified FAS.

The total AED drug load at first BRV administration (Baseline), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal), and the change from Baseline will be summarized by descriptive statistics. Change from Baseline is defined as: Total AED drug load at Visit 4 (Month 12) or Visit 4 (Month 12/Withdrawal) – total AED drug load at first BRV administration (Baseline).

The number of AEDs (including LEV, VNS use and BRV) taken per patient at first BRV administration (Baseline), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal), and change from Baseline will be summarized by descriptive statistics. The number of AEDs at first BRV administration (Baseline) will be equal to the number of AEDs at Study Entry as described in Section 6.4. Patients with VNS use at first BRV administration (Baseline) will be considered to have VNS use during the entire study and as such it will be counted as an AED at Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) as appropriate. The total number of AEDs at a visit is a count of the number of concomitant AEDs, LEV, or BRV that are being taken on the date of the visit with partial dates imputed as described in Section 4.2.2, plus any VNS use. Change from Baseline is defined as: Total number of AEDs at Visit 4 (Month 12) or Visit 4 (Month 12/Withdrawal) – total number of AEDs at first BRV administration (Baseline).

A by-patient listing of drug load data will be provided on the All Subjects Documented set. The listing will include the total drug load, number of AEDs (including LEV and BRV) taken per patient, the changes from Baseline, AEDs taken (including LEV or BRV), the daily dose per given product, DDD, drug load per AED, and frequency at each visit.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

This section is not applicable.

10 SAFETY ANALYSES

10.1 Extent of exposure

The duration of exposure of BRV (days) while in the study is calculated as:

Date of last administration of BRV while in the study – date of first BRV administration + 1.

For snapshot analyses, patients with missing date of last administration of BRV while in the study will be imputed using the date of data cut-off for the analysis. This assumes that patients still ongoing in the trial are still taking BRV.

All exposure analyses will be performed on the SS and the modified FAS.

Exposure will be summarized using descriptive statistics of the continuous variable duration of exposure (days). In addition, the following categories of duration of exposure (days) will show the number of patients with 1 day to <3 months BRV (1-<90 days), 3 months to <6 months BRV (90-<180 days), 6 months to <12 months BRV (180-<330 days), and ≥12 months BRV (≥330 days).

The number and percentage of patients receiving each daily BRV dose at Day 2, Day 7, Day 14, Day 21, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180, Day 240 and Day 330 will be

summarized in the following BRV dose categories (<= 10mg, >10 to <50mg, >=50mg to <100mg, >=100mg to <150mg, >=150mg to <=200mg and >200mg). In addition, the total number of patients receiving each Dose category at any time on the study will be presented. Day 1 will be equal to the first BRV administration date. Day 2 is considered as the starting dose due to some patients only receiving 1 dose (afternoon dose only) on Day 1.

Time to BRV maintenance dose will summarized descriptively and will be defined as:

Date of first intake of the BRV dose the patient remained on for the longest time during the treatment period – Date of first BRV administration.

If there is more than one dose which was taken for the equally longest time during the treatment period then the date of the first intake of the latter BRV dose will be used in the above calculation. If the patient has the same BRV dose twice (or more than twice) with a gap of BRV treatment in-between then the durations will not be added together to identify the BRV dose the patient remained on for the longest time; they will be considered separately. Similarly if the patient has the same BRV dose at least twice with another BRV dose in-between then the durations will not be added together; they will be considered separately.

A by-patient listing of exposure to BRV while in the study (including the start and stop dates of BRV, duration of exposure, and exposure category) will be provided on the All Subjects Documented set.

10.2 Adverse events

Adverse events and other safety relevant (OSR) information such as overdose or off label use, will be recorded using UCBs Pharmacovigilance database.

The UCB SafetyAdHoc Team will provide an ad hoc listing of the safety data with an additional variable named “Case Classification (All)” that allows identification of the “non-reportable” events. Only events that are identified as "reportable" (ie, where Case Classification (All) variable does not include "Non-Reportable") will be imported into the clinical database (SDTM). A list of MedDRA preferred terms (PTs) will be reviewed prior to database lock and used to identify OSR information. All PTs will be classified as AEs or OSR information. OSR information will not be included in the AE tables and listings, with the exception of the overview table for treatment-emergent adverse events (TEAE, see definition below) and OSR information, and the listing of AEs and OSR information that could not be reconciled.

A treatment-emergent adverse event (TEAE) is defined as an AE occurring on or after the date of first BRV administration.

An ADR is defined as a TEAE with an “as reported causality” as “related”, “unavailable” or missing.

In order to investigate the time to discontinuation of BRV due to ADRs, the time to discontinuation of BRV for all patients, will be calculated as:

Date of last administration of BRV while in the study – date of first BRV administration + 1

The date of last administration of BRV while in the study (both for completers and dropouts) and the date of first BRV administration will be taken from the CRF Study Termination (Completed Subject), Study Termination (Dropout), and First Administration of Drug pages. All patients who have an ADR with action=“Drug withdrawn” (recorded in the UCBs Pharmacovigilance

database) will be classed as having an event (discontinued BRV due to an ADR). All other patients will be censored. Time to discontinuation of BRV due to ADRs will be analyzed on the SS using Kaplan-Meier methods. The median time to discontinuation (days) of BRV due to ADRs (and 95% CI) will be presented along with the 25% and 75% quartiles (and 95% CI for the quartiles). The Kaplan-Meier plot and raw statistical procedure output will also be produced for the Kaplan-Meier analysis.

For each of the following event types, frequency tables of incidence based on the SS will be presented. The overview analysis of TEAEs and ADRs will also be repeated on the modified FAS:

- Overview of TEAEs and OSR information (including categories for any TEAE, serious TEAE, patient discontinuations of BRV due to TEAE [derived as any TEAEs with action= "Drug withdrawn"], drug-related TEAE [ADRs], all deaths [AEs leading to death]), and OSR information
- Overview of ADRs (including categories for any ADR, serious ADR, patient discontinuations of BRV due to ADRs [derived as any ADRs with action= "Drug withdrawn"], and all deaths [ADRs leading to death])
- TEAEs by MedDRA SOC and PT
- ADRs by MedDRA SOC and PT
- Non-serious TEAEs above reporting threshold of 5% of patients by MedDRA SOC and PT
- Non-serious ADRs above reporting threshold of 5% of patients by MedDRA SOC and PT
- TEAEs occurring in at least 5% of patients by MedDRA SOC and PT
- ADRs occurring in at least 5% of patients by MedDRA SOC and PT
- Serious TEAEs by MedDRA SOC and PT
- Serious ADRs by MedDRA SOC and PT
- Serious TEAEs – patient numbers
- Serious ADRs – patient numbers
- ADRs leading to permanent discontinuation of BRV by MedDRA SOC and PT
- TEAEs leading to death by MedDRA SOC and PT
- ADRs leading to death by MedDRA SOC and PT
- TEAEs by maximum relationship by SOC and PT

An AE Glossary (including the SOC, PT and reported term) will be provided separately for AEs and OSR information. In addition, the following by-patient listings for the All Subjects Documented set will be presented including the MedDRA SOC and PT, reported term, onset and outcome date, duration, seriousness, death, congenital defect, disability, hospitalization, life threatening, medically important event, outcome, relationship to study medication, and action taken with regards to study medication:

- All AEs (this listing will be repeated for patients aged <18 years only)

- All serious AEs
- All AEs leading to permanent discontinuation of BRV
- All deaths (AEs leading to death)
- OSR information
- AEs and OSR information that could not be reconciled (ie, AEs/OSR information for patient numbers that do not exist in the clinical database). This would be an ad hoc listing which will not be produced until after database lock if necessary.

10.3 Clinical laboratory evaluations

This section is not applicable as laboratory assessments are not recorded in this NIS study.

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

This section is not applicable as vital signs and physical findings are not recorded in this NIS study.

11 REFERENCES

Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. Epilepsy Behav. 2012;23(3):230-4.

Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia. 1998:39(1):81-8.

WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015. http://www.whocc.no/atc_ddd_index/ Accessed 17 Dec 2015.

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

12.3 Defined Daily Dose (DDD)

Defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. AEDs recorded on the study will have their DDD identified using their WHODD preferred term and the following website: http://www.whocc.no/atc_ddd_index/

Examples of common AEDs are provided in **Error! Reference source not found.**. Whilst these can be used as a guide all medications (these and any others recorded in the CRF) should be rechecked on the website and the appropriate DDD documented in the ADAM specifications.

Table 12–1: Defined Daily Doses for common AEDs

WHODD Preferred Term	WHO DDD (mg/day)
Acetazolamide	750
Brivaracetam	100
Carbamazepine	1000
Clobazam	20
Clonazepam	8
Clorazepate Dipotassium	20
Eslicarbazepine	800
Eslicarbazepine Acetate	800
Ethosuximide	1250
Felbamate	2400
Gabapentin	1800
Lacosamide	300
Lamotrigine	300
Levetiracetam	1500
Lorazepam	2.5
Mesuximide	900
Midazolam	15

Table 12–1: Defined Daily Doses for common AEDs	
WHODD Preferred Term	**WHO DDD (mg/day)**
Midazolam Hydrocholoride	15
Nitrazepam	5
Oxcarbazepine	1000
Perampanel	8
Phenobarbital	100
Phenytoin	300
Pregabalin	300
Primidone	1250
Stiripentol	1000
Sultiame	400
Tiagabine	30
Topiramate	300
Valproate	1500
Zonisamide	200

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

13.1 AMENDMENT 1

Rationale for the amendment

The SAP has been amended to implement any changes to the planned analyses made during the course of the study since the approval of the previous version of the SAP and to incorporate any clarifications to the text.

Modifications and changes

Global changes

The following global changes were applied to this SAP:

- Other safety relevant (OSR) added to abbreviations.
- MedDRA version updated to be September 2015
- Descriptions of definitions required for the interim snapshot reporting.
- Seizure freedom definitions updated in section 8.2.2
- Time to first seizure definition updated and table for its derivation added to section 8.2.3
- PRN added to the list of daily dose calculations in table 8-4.
- Adverse event definition expanded upon.
- Derivation of OSR events clarified
- ADR definition expanded upon
- Classification of patients with AEs split further.
- Overview of adverse events summary rewritten.
- Flags for OSR events added to listing of AEs

Specific changes

Change #1

List of abbreviations.

The following abbreviation was added

OSR	other safety relevant

Change #2

3.2.3 Date of last administration of BRV

If the date is missing, then use the last end date from the BRV Medication CRF page (applying the imputation of partial end dates rules as required). If that date is also missing then use the date of first BRV administration as collected on the First Administration of Drug CRF page. If this start date is partial, use a day of 01 if month and year are present, or 01 January if only year is present. If all of the above are missing, then it is assumed the patient did not take BRV.

Has been changed to:

For the snapshot analyses described in section 4.3, patients ongoing in the study will not yet have a date of last administration of BRV recorded. For these patients the date of last administration of BRV will be imputed using the date of the data cut off so that an estimate of the exposure to date can be calculated.

For patients who have completed or withdrawn from the study, if the date of last administration is missing, then the last end date from the BRV Medication CRF page (applying the imputation of partial end dates rules as required) will be used. If that date is also missing then the date of first BRV administration as collected on the First Administration of Drug CRF page will be used. If this start date is partial, use a day of 01 if month and year are present, or 01 January if only year is present. If all of the above are missing, then it is assumed the patient did not take BRV.

Change #3

3.8 Coding dictionaries

Medications will be coded using the March 2016 version of World Health Organization Drug Dictionary (WHODD).

Has been changed to:

Medications will be coded using the September 2015 version of World Health Organization Drug Dictionary (WHODD).

Change #4

4.3 Interim analyses and monitoring

- A first snapshot analysis is to be performed with a data cut-off date approximately at the end of 2016 or when 80 patients have completed Visit 2 (Month 3), whichever occurs first. All patients with available data in the database will be included in the analyses.

- A second snapshot analysis is to be performed with a data cut-off date approximately at the end of 2017, depending on recruitment status.

All planned TFLs identified in the SAP and Mock TFL shells will be delivered for the snapshot analyses including all visits in the database at time of the snapshot cut off. As data is entered in an ongoing way throughout the study, any data entered after the data cleaning cut off (but prior to the data extract) for each snapshot may not be clean. Any data discrepancies observed will be discussed and their impact on the analysis documented.

Has been changed to:

- A first snapshot analysis is to be performed with a data cut-off date approximately at the end of 2016 or when 80 patients have completed Visit 2 (Month 3), whichever occurs first. All patients with available data in the database will be included in the analyses. A subset of the end of study TFLs will be produced.
- A second snapshot analysis is to be performed with a data cut-off date approximately at the end of 2017, depending on recruitment status. If the recruitment schedule results in there not being enough additional data from the previous snapshot then the snapshot cut-off date may be delayed to ensure approximately 200 patients with Visit 2 (Month 3). It is expected that all TFLs identified in the SAP and Mock TFL shells will be delivered including all visits in the database at the time of the snapshot cut off.

As data is entered in an ongoing way throughout the study and cleaning is ongoing, data discrepancies in the snapshot analyses are possible. Any data discrepancies observed in the database at the time of the snapshot analyses will be discussed and their impact on the analysis documented.

Change #5

4.8 Examination of subgroups

- Age at Visit 1 (<65 and ≥65 years).
- Time since first diagnosis of epilepsy (0-<1 years, 1-<5 years, 5-10 years, >10 years): Defined in Section 6.2
- Number of concomitant Baseline AEDs (0, 1, ≥2AEDs) : Defined in Section 6.4
- Number of Historical AEDs (0, 1, 2, ≥3): Defined in Section 6.4
- Historical Levetiracetam (LEV) use (Yes, No): Defined in Section 6.4
- 28-day Baseline all seizures frequency (≤5, >5-10, >10) : Defined in Section 8.2.2.1

Has been changed to:

- Age at Visit 1 (<65 and ≥65 years).
- Time since first diagnosis of epilepsy (0-<1 years, 1-<5 years, 5-10 years, >10 years): Defined in Section 6.2
- Number of AEDs at Study Entry (0, 1, ≥2AEDs) : Defined in Section 6.4
- Number of Historical AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4

- Historical Levetiracetam (LEV) use (Yes, No): Defined in Section 6.4
- Number of Lifetime AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- 28-day Baseline all seizures frequency (≤5, >5-10, >10) : Defined in Section 8.2.2.1

Change #6

6.4 Prior and concomitant medications

Concomitant Baseline medications are a subset of concomitant medications, defined as those being taken at study entry (on the same day as Visit 1). Concomitant medications are medications taken at least 1 day in common with the study medication dosing period. In other words, those that started on or prior to Visit 1, and have an end date on or after Visit 1 or are ongoing.

Note that only relevant concomitant medications will be recorded on the CRF.

Has been changed to:

Concomitant Baseline medications are defined as those being taken at study entry (on the same day as Visit 1). Concomitant medications are medications taken at least 1 day in common with the study medication dosing period. In other words, those that started on or prior to the date of first BRV administration, and have an end date on or after the date of first BRV administration or are ongoing; or those starting after 1st BRV administration and on or before last BRV administration.

Change #7

6.4 Prior and concomitant medications

Patients documented as having used a vagus nerve stimulation (VNS) magnet will be considered as having active use at Visit 1 (Baseline) and during the study. Hence, VNS use is counted as an AED for Baseline concomitant AEDs. As historical AEDs are defined as medications discontinued prior to Visit 1 (Baseline), VNS use at Visit 1 will not be counted as a historical AED. VNS use, number of historical AEDs, number of concomitant Baseline AEDs, and LEV use will be summarized as follows:

- Number of patients with/without a VNS magnet
- Number of patients with historical and concomitant Baseline LEV use
- Number of historical AEDs, presented using summary statistics and the following categories (0, 1, 2, and ≥3)
- Number of concomitant Baseline AEDs, presented using summary statistics and the following categories (0, 1, and ≥2)

The summaries above will be repeated for the subgroups of patients with and without VNS use, and with and without historical LEV.

The following listings will be provided:

Has been changed to:

Patients documented as having used a vagus nerve stimulation (VNS) magnet will be considered as having active use at Visit 1 (Baseline) and during the study. Hence, VNS use is counted as an AED for AEDs taken at study entry. As historical AEDs are defined as medications discontinued prior to Visit 1 (Baseline), VNS use at Visit 1 will not be counted as a historical AED. Lifetime AEDs are defined as a sum of the historical AEDs and AEDs taken at study entry. As LEV can be included in both historical AEDs and AEDs at study entry, it will only be counted once in the calculation of Lifetime AEDs.

VNS use, number of historical AEDs, number of AEDs at study entry, Lifetime AEDs and LEV use will be summarized as follows:

- Number of patients with/without a VNS magnet
- Number of patients with historical and LEV use at study entry
- Number of historical AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)
- Number of AEDs at study entry, presented using summary statistics and the following categories (0, 1, and ≥2)
- Number of Lifetime AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)

The summaries above will be repeated for the subgroups of patients with and without VNS use, and with and without historical LEV.

The following listings will be provided:

Change #8

8.2.2 Seizure frequency related variables

- Seizure freedom (Yes, No) will be defined using two methods as shown in Table 8–1. Visit 4 (Month 12/Withdrawal) will not be summarized for seizure freedom.

Table 8-1: Derivation of seizure freedom

Patient Classification at Visit	Seizure freedom – Discontinuations counted as not seizure free	Seizure freedom – Discontinuations counted as missing
1. Patient had a seizure (including all seizure types) on or after Visit 1 and on or before the Visit date.	No	No
2. Patient discontinued BRV or terminated the study prior to the visit's target day [a]	No	Missing
3. Patient had missing seizure data at the visit (or missed the visit) but had not discontinued BRV or terminated the study prior to the visit's target day [a]	Missing	Missing
4. Patient meet none of the above classifications	Yes	Yes

[a] The target day for each visit is: Visit 2 (Month 3) = Day 90, Visit 3 (Month 6) = Day 180, and Visit 4 (Month 12) = Day 330.

Has been changed to:

- Seizure freedom (Yes, No) will be defined using two methods as shown in Table 8–1. The first method considers patients who withdraw prior to their 1st seizure as Not seizure free. The 2nd is a less conservative method which considers patients who withdraw prior to their 1st seizure as missing. Visit 4 (Month 12/Withdrawal) will not be summarized for seizure freedom.

Table 8-1: Derivation of seizure freedom

Patient Classification at Visit (patients are assigned to the first category they fall into)	Seizure freedom – Discontinuations counted as not seizure free	Seizure freedom – Discontinuations counted as missing
0. Patients had a seizure before 1st BRV dose	Missing	Missing
1. Patient had a seizure on or after 1st BRV dose and on or before the visit date derived using the following conditions. First_seizure_date = Date of first seizure or if date of first seizure is missing but patient has seizures recorded at a visit, then assign first_seizure_date as the date of the visit prior to the earliest visit with seizures recorded a) Visit date present and First_seizure_date is on or after 1st BRV and on or before the Visit date b) Visit date is missing (either due to patient ongoing in study or visit missed) and First_seizure_date is on or after 1st BRV and on or before the visits target day [a])	No	No
2. Patient discontinued BRV or terminated the study prior to the visit's target day [a]	No	Missing
3. Patient had missing seizure data at the visit (or missed the visit) but had not discontinued BRV or terminated the study prior to the visit's target day [a] Note: If a patient is ongoing in the study and had not got to the visit yet, they are treated in the same way as having missed visit.	Missing	Missing
4. Patient met none of the above classifications and patient has the visit present	Yes	Yes

[a] The target day for each visit is: Visit 2 (Month 3) = Day 90, Visit 3 (Month 6) = Day 180, and Visit 4 (Month 12) = Day 330. For Month 12 assessments, seizure freedom will be analyzed for completers only. Therefore assign missing to all patients who withdraw for the Month 12 analyses.

Change #9

8.2.3 Time to first seizure

The time to the first seizure (days) will be calculated as:

Date of first seizure in the trial – date of first BRV administration + 1

For patients attending a visit but with missing seizure data, they will be censored at the date of the last visit without missing seizure information. Patients missing an entire visit will still have their seizure information recorded at the next available visit and so no action will be taken. For patients discontinuing BRV study medication before experiencing their first seizure, they will be censored at the date of last administration of BRV while in the study. For patients with no recorded seizures and still on BRV study medication, they will be censored at the date of last visit

Has been changed to:

The time to the first seizure (days) will be calculated as:

Date of first seizure in the trial – date of first BRV administration + 1

If the exact date of first seizure cannot be determined but the patient has had seizures recorded post Visit 1, then the patient will still be counted as having an event using a conservative approach as shown in Table 8–2 .

For patients with no evidence of seizures, the following sequential approach will be taken which is further detailed in Table 8–2:

1. For patients attending a visit but with missing seizure data, they will be censored at the date of the last visit prior to the visit with the missing seizure information.
2. For patients discontinuing BRV study medication before experiencing their first seizure, they will be censored at the date of last administration of BRV while in the study.
3. For patients with no recorded seizures and still on BRV study medication, they will be censored at the date of last visit.

As the approach used is very conservative, if there are a lot of patients censored in the early visits due to missing data or with early events due to missing data, a sensitivity analysis may be performed.

Table 8-2: Derivation of time to first seizure

Missing date of first seizure but seizures recorded				No evidence of seizures on the study			
V2	**V3**	**V4**	**Date used**	**V2**	**V3**	**V4**	**Date used**
M	M	>0	E-V1/1BRV [a]	M	M	M	C-V1
M	>0	NA	E-V1/1BRV [a]	0	M	M	C-V2
>0	NA	NA	E-V1/1BRV	M	0	M	C-V1
0	>0	NA	E-V2	M	M	0	C-V1
0	0	>0	E-V3	0	0	M	C-V3
M	-	>0	E-V1/1BRV [a]	0	M	0	C-V2

Table 8-2: Derivation of time to first seizure							
Missing date of first seizure but seizures recorded				**No evidence of seizures on the study**			
V2	**V3**	**V4**	**Date used**	**V2**	**V3**	**V4**	**Date used**
0	-	>0	E-V2	M	0	0	C-V1
-	>0	NA	E-V1/1BRV [a]	0	0	0	C-V4
-	M	>0	E-V1/1BRV [a]	0	Disc BRV	NA	C- Last BRV
				M	Disc BRV	NA	C-V1

[a] The rationale behind using V1/1BRV in this scenario is based on it being unknown when exactly between V1 and V4 that the first seizure event occurred. V1/1BRV is more conservative and hence will be used, however a sensitivity analysis may be performed if there are a lot of patients with missing data.

Note: M=patient is missing seizure data at this visit but attended the visit, - = patient missed entire visit, NA=Visit is not applicable/not required to be considered in this scenario, V=Visit, C=Censor, E=Event, 1BRV= Date of first dose of BRV, Last BRV= date of last dose of BRV.

Note: V1/1BRV implies the date of the first dose of BRV should be used if it is later than V1 to avoid negative time to events and under-reporting of potential seizure events. For patients with no evidence of seizures on the study, negative censoring times are acceptable as it is equivalent to censoring the patient on Day 1.

Change #10

Table 8-4: Daily dose calculation		
Frequency	**Description**	**Multiply dose per intake by:**
PRN	As needed	Excluded from calculation

The row shown above was added to Table 8-4

Change #11

10.1 Extent of exposure

The duration of exposure of BRV (days) while in the study is calculated as:

Date of last administration of BRV while in the study – date of first BRV administration + 1

Exposure will be summarized on the SS using descriptive statistics of the continuous variable duration of exposure (days). In addition, the following categories of duration of exposure (days) will show the number of patients with 1 day to <3 months BRV (1-<90 days), 3 months to <6 months BRV (90-<180 days), 6 months to <12 months BRV (180-<330 days), and ≥12 months BRV (≥330 days).

Has been changed to:

The duration of exposure of BRV (days) while in the study is calculated as:

Date of last administration of BRV while in the study – date of first BRV administration + 1.

For snapshot analyses, patients with missing date of last administration of BRV while in the study will be imputed using the date of data cut-off for the analysis. This assumes that patients still ongoing in the trial are still taking BRV.

Exposure will be summarized on the SS using descriptive statistics of the continuous variable duration of exposure (days). In addition, the following categories of duration of exposure (days) will show the number of patients with 1 day to <3 months BRV (1-<90 days), 3 months to <6 months BRV (90-<180 days), 6 months to <12 months BRV (180-<330 days), and ≥12 months BRV (≥330 days).

The number and percentage of subjects receiving each daily BRV dose at Day 2, Day 7, Day 14, Day 21, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180 and Day 240 will be summarized in the following BRV dose categories (<= 10mg, >10 to <50mg, >=50mg to <100mg, >=100mg to <150mg, >=150mg to <=200mg and >200mg) the following days for all patients in the Safety Set. In addition, the total number of patients receiving each Dose category at any time on the study will be presented. Day 1 will be equal to the first BRV administration date. Day 2 is considered as the starting dose due to some patients only receiving one dose (afternoon dose only) on Day 1.

Time to BRV maintenance dose will summarized descriptively for all patients in the safety set and will be defined as:

Date of first intake of the highest BRV dose during the study – Date of first BRV administration

Change #12

10.2 Adverse Events

Adverse events will be recorded using UCBs Pharmacovigilance database. A treatment-emergent adverse event (TEAE) is defined as an AE occurring on or after the date of first BRV administration.

ADRs will be defined as AEs with an "as reported causality" as "related", "unavailable" or missing by the investigator. Since an ADR is an AE related to the medication to be investigated (BRV), all reported ADRs are considered treatment-emergent and will be included in the analysis.

Has been changed to:

Adverse events (referred to in this section as clinical AEs) and other safety relevant (OSR) events such as overdose or off label use, will be recorded using UCBs Pharmacovigilance database. A list of MedDRA preferred terms will be reviewed prior to database lock and used to define OSR events.

A treatment-emergent adverse event (TEAE) is defined as an AE occurring on or after the date of first BRV administration.

An ADR is defined as :

- An OSR event with an "as reported causality" as "related" (OSR ADR)
- A clinical AE with an "as reported causality" as "related", "unavailable" or missing (Clinical ADR).

Since an ADR is an AE related to the medication to be investigated (BRV), all reported ADRs (both clinical ADRs and OSR ADRs) are considered treatment-emergent and will be included in the ADR table summaries. Any treatment-emergent OSR events which do not have an "as reported causality" of "related" are classed as OSR non-ADRs.

Patients will be classified further into:

1. Patients with an OSR non-ADR and no clinical ADRs
2. Patients with an OSR non-ADR and at least one clinical ADR.

If a patient has more than one OSR non-ADR then they will be counted once in the patient count and percentage but with all their OSR non-ADRs in the corresponding event count.

An example for 5 patients is shown below to clarify how this classification will be applied.

Row ID	Patient ID	Clinical AE or OSR event	Relationship	ADR or non-ADR	Category 1= Patients with an OSR non-ADR and no clinical ADRs Category 2=Patients with an OSR non-ADR and at least one clinical ADR.
1	[redacted]	OSR event	Unavailable	non-ADR	Category 2. OSR non-ADR (row 1) and at least one clinical ADR (row 2). The OSR non-ADR count for this patient is 1 event.
2	[redacted]	Clinical AE	Related	ADR	
3	[redacted]	OSR event	Related	ADR	Category 2. OSR non-ADR (row 5) and at least one clinical ADR (row 4). Note row 3 is not classed as an OSR non-ADR as it is related and hence already reported in the tables of ADRs. Row 6 is not relevant to the classification as it is a not related (non-ADR) clinical AE. The OSR non-ADR count for this patient is 1 event.
4	[redacted]	Clinical AE	Related	ADR	
5	[redacted]	OSR event	Unavailable	non-ADR	
6	[redacted]	Clinical AE	Not related	non-ADR	
7	[redacted]	OSR event	Unavailable	non-ADR	Category 1. OSR non-ADR (row 7) and no clinical ADR. Note: row 8 is not an ADR hence the patient has no clinical ADRs. The OSR non-ADR count for this patient is 1 event.
8	[redacted]	Clinical AE	Not related	non-ADR	
9	[redacted]	OSR event	Unavailable	non-ADR	Category 2. OSR non-ADR (row 9) and at least one clinical ADR (row 10). The OSR non-ADR count for this patient is 1 event.
10	[redacted]	Clinical AE	Unavailable	ADR	
11	[redacted]	OSR event	Unavailable	non-ADR	Category 1. OSR non-ADR (row 11 and row 13) and no clinical ADR. The OSR non-ADR count for this patient is 2 events.
12	[redacted]	Clinical AE	Not related	non-ADR	
13	[redacted]	OSR event	Unavailable	non-ADR	

Change #13

10.2 Adverse events

Overview of TEAEs (including any TEAE, serious TEAE, patient discontinuations of BRV due to TEAE [derived as any TEAEs with action= "Drug withdrawn"], drug-related TEAE [ADRs], and all deaths [AEs leading to death])

Has been changed to:

Overview of TEAEs (including any TEAE, serious TEAE, patient discontinuations of BRV due to TEAE [derived as any TEAEs with action= "Drug withdrawn"], drug-related TEAE [ADRs], all deaths [AEs leading to death], "OSR non-ADRs and no clinical ADR" and "OSR non-ADRs and at least one clinical ADR")

Change #14

10.2 Adverse events

An AE Glossary (including the SOC, PT and reported term) will be provided. In addition, the following by-patient listings of AEs including a flag for TEAEs and/or ADRs, for the All Subjects Documented set will be presented including the MedDRA SOC and PT, reported term, onset and outcome date, duration, seriousness, death, congenital defect, disability, hospitalization, life threatening, medically important event, outcome, relationship to study medication, and action taken with regards to study medication:

Has been changed to:

An AE Glossary (including the SOC, PT and reported term) will be provided. In addition, the following by-patient listings of AEs (including flags for TEAEs, ADRs and OSR events), for the All Subjects Documented set will be presented including the MedDRA SOC and PT, reported term, onset and outcome date, duration, seriousness, death, congenital defect, disability, hospitalization, life threatening, medically important event, outcome, relationship to study medication, and action taken with regards to study medication:

13.2 AMENDMENT 2

Rationale for the amendment

The SAP has been amended to implement changes to the planned analyses made during the course of the study since the approval of the previous version of the SAP and to incorporate any clarifications to the text.

Modifications and changes

Change #1

3.2.2 Visit 4, Month 12/Withdrawal Visit

From:

Patients with early study termination (ie, those who complete the Study Termination [Dropout] CRF page), will have their Visit 4 data entered prior to the preferred visit window for Month 12 of greater than 330 days after date of first BRV administration. Therefore, Visit 4 will be analyzed as follows depending on the objective and variable being analyzed:

- Visit 4 (Month 12): Including only patients who are study completers (ie, complete the Study Termination NIS (Completed Subject) CRF form
- Visit 4 (Month 12/Withdrawal): Including all data recorded at Visit 4 (ie, completers or patients who withdraw early)

To:

Patients with early study termination (ie, those who complete the Study Termination [Dropout] CRF page), will have their Visit 4 (Month 12/Withdrawal) visits prior to the preferred visit window for Month 12 of greater than 330 days after date of first BRV administration. Patients completing the study (ie, those who complete the Study Termination NIS [Completed Subject] CRF form), will have their Visit 4 (Month 12/Withdrawal) visits within the preferred visit window for Month 12 of greater than 330 days after date of first BRV administration. Therefore, Visit 4 will be analyzed as follows depending on the objective and variable being analyzed:

- Visit 4 (Month 12): Including only patients who are study completers
- Visit 4 (Month 12/Withdrawal): Including all data recorded at Visit 4 (ie, completers or patients who withdraw early)

In addition, Visit 4 (Month 12/Withdrawal) visits that correspond to scheduled visits will be included in the counts for the scheduled visits to which they correspond. To be classed as corresponding to the scheduled visit, the withdrawal visit must fall into the windows provided below and the patient have no scheduled visit already available. Only the variables below will have the mapping of withdrawal visits applied.

Variables	V2, M3	V3, M6
Disposition (Patients attending each visit)	30-135	136-329
Seizure Frequency	30-135	136-329
QOLIE	30-135	136-329
CGIC/PGIC	30-135	136-329
EpiTrack	No mapping as no scheduled visit	150-210

Change #2

5.1 Subject disposition

From:

- Number and percentage of patients attending each scheduled visit

To:

- Number and percentage of patients attending each scheduled visit (including mapping of withdrawal visits as described in section 3.2.2)

Change #3

8.2.2.1 Initial processing of diary data

From:

Partial-onset seizures frequency will only be calculated at visits attended and with seizure data recorded, hence a patient withdrawing after Visit 2 and having an end of Observation Period (withdrawal visit) data recorded for Visit 4 (instead of a Month 12) will only have data available at Visit 1 (Baseline), Visit 2 (Month 3) and Visit 4 (Month 12/Withdrawal).

To:

Partial-onset seizures frequency will only be calculated at visits attended and with seizure data recorded. For seizure frequency summaries, data recorded at Visit 4 (Month 12/Withdrawal) visit will be mapped to the appropriate scheduled visits as described in section 3.2.2. No mapping will be performed for Seizure freedom as the derivation is date based rather than visit based.

Change #4

8.3.1.2 Analysis of QOLIE-31-P scores

From:

Descriptive statistics will be presented for QOLIE-31-P: 7 multi-item subscales, the health status item, and total score, and the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) for the FAS. As described in Section 3.2.2, Visit 4 (Month 12) will only include patients completing the study.

To:

Descriptive statistics will be presented for QOLIE-31-P: 7 multi-item subscales, the health status item, and total score, and the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) for the FAS. As described in Section 3.2.2, Visit 4 (Month 12/Withdrawal) visits will be mapped to the appropriate scheduled visit and Visit 4 (Month 12) will only include patients completing the study.

Change #5

8.3.2 EpiTrack

From:

Descriptive statistics will be provided for the FAS of the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests (after the raw scores have been translated into points). The changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12) will also be displayed.

To:

Descriptive statistics will be provided for the FAS of the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests (after the raw scores have been translated into points). Visit 4 (Month 12/Withdrawal) visits will be mapped to Visit 3 (Month 6) if they are within the windows described in Section 3.2.2. EpiTrack results by visit and the changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12) will be displayed.

Change #6

8.3.3 Clinical Global Impression of Change (CGIC) and Patient's Global Impression of Change (PGIC)

From:

The number and percentage of patients with each CGIC and PGIC rating and who had improved, had no change, or worsened at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) will be presented on the FAS.

To:

The number and percentage of patients with each CGIC and PGIC rating and who had improved, had no change, or worsened at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit

4 (Month 12/Withdrawal) will be presented on the FAS. Visit 4 (Month 12/Withdrawal) visits will be mapped as described in Section 3.2.2.

Change #7

12.3 Defined Daily Dose

Updated Table 12-1 to include the Compound Perampanel with ATC code =N03AX22 and WHO DDD (mg/day)=8.

13.3 AMENDMENT 3

Rationale for the amendment

The SAP has been amended to implement any changes to the planned analyses made during the course of the study since the approval of the previous version of the SAP and to incorporate any clarifications to the text. In particular the SAP was amended to repeat analyses on the modified FAS in order to provide summaries of demography, baseline characteristics, concomitant medications, effectiveness and safety for patients treated according to the approved SmPC during their Observation Period. This will provide an analysis representing the on-label use of BRV.

Modifications and changes

Global changes

Corrections to use "Patient" instead of "Subject" throughout the text, as appropriate, were made, except titles from the SAP template or populations. The UCB style guide indicates to use numbers instead of spelling them out so this change was made throughout the document.

Specific changes

Change #1

List of abbreviations.

The following abbreviation were added

BID	"bis in die"/twice daily
NA	Not applicable

Change #2

1 Introduction

From:

This SAP is based upon, and assumes familiarity with, the Final Protocol dated 04 Nov 2015.

To:

This SAP is based upon, and assumes familiarity with, the Final Protocol Amendment dated 25 Oct 2018.

Change #3

2.3 Study design and conduct

From:

It is planned to include 430 patients in the study.

To:

It is planned to include 530 patients in the study.

Change #4

2.4 Determination of sample size

From:

A sample size of 430 patients was chosen for this study in order to obtain 385 patients in the Full Analysis Set (FAS), which allows for approximately 10% of patients to not be included.

When the sample size is 385, a 2-sided 95% confidence interval (CI) for a single proportion using the large sample normal approximation will extend 0.05 from the observed proportion for an expected proportion of 0.50. As an example, given an observed retention rate of 50%, a sample size of 385 patients would give a 2-sided 95% CI of 45% to 55% based on the large sample normal approximation to the binomial distribution.

It is, therefore, planned to have 430 patients, and withdrawals will not be replaced.

To:

Initially, a sample size of 430 patients was chosen for this study in order to obtain 385 patients in the Full Analysis Set (FAS), which allows for approximately 10% of patients to not be included.

When the sample size is 385, a 2-sided 95% confidence interval (CI) for a single proportion using the large sample normal approximation will extend 0.05 from the observed proportion for an expected proportion of 0.50. As an example, given an observed retention rate of 50%, a sample size of 385 patients would give a 2-sided 95% CI of 45% to 55% based on the large sample normal approximation to the binomial distribution.

However, since the first 100 patients were all enrolled at sites in Germany in early 2016 and the enrollment in that country was closed, it was believed that ongoing enrollment in other countries would be following different best practices in BRV usage, which could lead to wide variation in this NIS. For this reason, 100 additional patients are planned to be enrolled to obtain 385 patients in the FAS at non-German sites.

It is, therefore, planned to have 530 patients, and withdrawals will not be replaced.

Change #5

3.2.2 Visit 4, Month 12/Withdrawal Visit

From:

Patients with early study termination (ie, those who complete the Study Termination [Dropout] CRF page), will have their Visit 4 (Month 12/Withdrawal) visits prior to the preferred visit window for Month 12 of greater than 330 days after date of first BRV administration. Patients completing the study (ie, those who complete the Study Termination NIS [Completed Subject] CRF form), will have their Visit 4 (Month 12/Withdrawal) visits within the preferred visit

window for Month 12 of greater than 330 days after date of first BRV administration. Therefore, Visit 4 will be analyzed as follows depending on the objective and variable being analyzed:

- Visit 4 (Month 12): Including only patients who are study completers

…

EpiTrack	No mapping as no scheduled visit	

To:

Patients with early study termination (ie, those who complete the Study Termination [Dropout] CRF page), will have their Visit 4 (Month 12/Withdrawal) visits prior to the preferred visit window for Month 12 of greater than or equal to 330 days after date of first BRV administration. Patients completing the study (ie, those who complete the Study Termination NIS [Completed Subject] CRF form), will have their Visit 4 (Month 12/Withdrawal) visits within the preferred visit window for Month 12 of greater than or equal to 330 days after date of first BRV administration. Therefore, Visit 4 will be analyzed as follows depending on the objective and variable being analyzed:

- Visit 4 (Month 12): Including only patients who are study completers with a Visit 4 within the preferred visit window for Month 12 of greater than 330 days after the date of first BRV administration.

…

EpiTrack	No mapping as no scheduled visit	150-210

Change #6

3.3 Definition of Baseline values

From:

In this NIS, Baseline is defined as the data collected at Visit 1. For seizure frequency variables, Baseline is defined in Section 8.2.2.1.

To:

In this NIS, Baseline is defined as the data collected at Visit 1. For prior and concomitant medications and for AED drug load, Baseline is defined as first BRV administration. For seizure frequency variables, Baseline is defined in Section 8.2.2.1.

Change #7

3.5 Analysis sets

From:

- BRV is administered as an adjuvant therapy, defined as
  - patient receiving at least 1 concomitant AED at Baseline and at each post-Baseline documented visit.

– patient does not have a protocol violation of Selection Criterion # 6

To:

- BRV doses were administered in 2 equally divided doses (BID). According to when the first dose or last dose is administered, other administration schemes can occur. Hence any patients receiving BRV not divided into 2 equally doses will be reviewed during the DEM to determine whether they are taking BRV per SmPC.
- BRV is administered as an adjuvant therapy, defined as
  - patient receiving at least 1 concomitant AED at Baseline and at each post-Baseline documented visit.
  - patient does not have a protocol violation of Selection Criterion # 6

Modified FAS listings to investigate compliance with the approved SmPC will be created and reviewed at the DEM prior to database lock in order to determine which patients will be included in the modified FAS. If the number of patients in the modified FAS is sufficiently different to that in the FAS, then key demographic, effectiveness and safety tables will be repeated on the modified FAS.

Change #8

3.8 Coding dictionaries

From:

Adverse drug reactions will be coded using version 18.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the September 2015 version of World Health Organization Drug Dictionary (WHODD).

To:

Adverse drug reactions will be coded using version 20.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the September 2017 version of World Health Organization Drug Dictionary (WHODD).

Change #9

4.3 Interim analyses and data monitoring

Due to the extension in patient recruitment on the study, there will be an increase in sample size and a third snapshot analysis to take place in 2019. The following paragraph was added:

- A third snapshot analysis will be performed with a data cut-off date on 28 Nov 2019. All TFLs identified in the SAP and Mock TFL shells will be delivered including all visits in the database at the time of the snapshot cut off.

Change #10

4.6 Use of subsets of subjects

From:

All effectiveness analysis will be performed on the FAS. In addition, to provide an estimate of effectiveness for patients using BRV per the approved SmPC, retention at 12 months will be repeated using the modified FAS.

To:

All effectiveness analysis will be performed on the FAS and the modified FAS to an estimate of effectiveness for patients using BRV per the approved SmPC.

Change #11

6 Demographics and other baseline disease characteristics

From:

All demography, Baseline disease characteristics, and historical and concomitant medication summaries will be presented on the SS. Demography will be also presented on the All Subjects Documented set. Listings of all data will be presented on the All Subjects Documented set.

To:

All demography, Baseline disease characteristics, and historical and concomitant medication summaries will be presented on the SS and modified FAS, except for subgroup analyses that will only be presented on the SS. Demography will be also presented on the All Subjects Documented set. Listings of all data will be presented on the All Subjects Documented set.

Change #12

6.4 Prior and concomitant medications

From:

Medications classified as AEDs or non-AEDs in the CRF, will be reviewed during the DEM to ensure correct classification. In addition, historical and concomitant medications will be reviewed to ensure documentation in the correct CRF pages. Historical medications are defined as medications discontinued prior to Visit 1 (Baseline). Concomitant Baseline medications are defined as those being taken on the same day as at study entry (on the same day as Visit 1). Concomitant medications are medications taken at least 1 day in common with the study medication dosing period. In other words, those that started on or prior to the date of first BRV administration, and have an end date on or after the date of first BRV administration or are ongoing; or those starting after the 1st BRV administration and on or before last BRV administration.

Non-AED historical medications, those stopped before Visit 1 (Baseline), should not be collected in the CRF.

As there are snapshot analyses throughout the study and data entry is ongoing, any non-coded terms at the time of reporting will report the WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3] and PT as UNCODED in the tables and listings.

The number and percentage of patients with each of the following medication types will be summarized overall and by WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3] and PT.

- Number and percentage of patients with AED concomitant medications (including LEV)
- Number and percentage of patients with non-AED concomitant medications

Where necessary, PTs may be collapsed into AED PT categories for study reporting and where applied this will be added as a footnote on the output. In addition, LEV use will be combined with other AED medications and reported in the table of AED concomitant medications.

Patients documented as having used a vagus nerve stimulation (VNS) magnet will be considered as having active use at Visit 1 (Baseline) and during the study. Hence, VNS use is counted as an AED for AEDs taken at study entry. As historical AEDs are defined as medications discontinued prior to Visit 1 (Baseline), VNS use at Visit 1 will not be counted as a historical AED. Lifetime AEDs are defined as a sum of the historical AEDs and AEDs taken at study entry. As LEV can be included in both historical AEDs and AEDs at study entry, it will only be counted once in the calculation of Lifetime AEDs.

To:

Medications classified as AEDs or non-AEDs in the CRF, will be reviewed during the DEM to ensure correct classification. In addition, historical and concomitant medications will be reviewed to ensure documentation in the correct CRF pages. Historical medications are defined as medications discontinued prior to the date of first BRV administration. Medications at study entry are defined as those being taken on the same day as first BRV administration. Concomitant medications are medications taken at least 1 day in common with the study medication dosing period. In other words, those that started on or prior to the date of first BRV administration, and have an end date on or after the date of first BRV administration or are ongoing; or those starting after the first BRV administration and on or before last BRV administration.

Non-AED historical medications, those stopped before the date of first BRV administration, should not be collected in the CRF.

As there are snapshot analyses throughout the study and data entry is ongoing, any non-coded terms at the time of reporting will report the WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3] and PT as UNCODED in the tables and listings.

The number and percentage of patients with each of the following medication types will be summarized overall and by WHODD Anatomical Main Group [Level 1], Pharmacological Subgroup [Level 3] and PT.

- Number and percentage of patients with AED concomitant medications (including LEV)
- Number and percentage of patients with non-AED concomitant medications

Where necessary, PTs may be collapsed into AED PT categories for study reporting and where applied this will be added as a footnote on the output. In addition, LEV use will be combined with other AED medications and reported in the table of AED concomitant medications.

Patients documented as having used a vagus nerve stimulation (VNS) magnet will be considered as having active use on the date of first BRV administration and during the study. Hence, VNS use is counted as an AED for AEDs taken at study entry. As historical AEDs are defined as medications discontinued prior to the date of first BRV administration, VNS use at study entry will not be counted as a historical AED. Lifetime AEDs are defined as a sum of the historical AEDs and AEDs taken at study entry. As LEV can be included in both historical AEDs and AEDs at study entry, it will only be counted once in the calculation of Lifetime AEDs.

Change #13

8 Effectiveness Analysis

The following was added:

All effectiveness analyses will be performed on the FAS and the modified FAS, except subgroup analyses that will only be performed on the FAS.

Change #14

8.1.1 Retention at 12 Months

From:

- Date of study termination < date of first BRV administration + 330 days
- Date of last administration of BRV while in the study < date of first BRV administration + 330 days

Otherwise, patients meeting either condition will be categorized as not having 12 months BRV retention.

To:

- Date of study termination < date of first BRV administration + 330 days
- Date of last administration of BRV while in the study < date of first BRV administration + 330 days

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 12 months BRV retention.

Change #15

8.1.2 Sensitivity analysis of the primary variable retention at 12 months

From:

In addition, a Kaplan-Meier analysis of time to discontinuation of BRV or study termination will be provided on the FAS. Time to discontinuation of BRV or study termination will be calculated as:

Minimum of (Date of last administration of BRV while in the study, Date of study termination) – date of first BRV administration + 1

All patients completing the study will be censored at the date of study termination. All other patients will be considered as having an event.

To:

In addition, a Kaplan-Meier analysis of time to discontinuation of BRV or study termination will be provided on the FAS and the modified FAS. Time to discontinuation of BRV or study termination will be calculated as:

Minimum of (Date of last administration of BRV while in the study, Date of study termination) – date of first BRV administration + 1

A patient will be considered as having an event if the patient discontinues from the study (Study Termination [Dropout] CRF page completed) or if the patient is not prescribed Brivaracetam after exiting the study (ie, answer to the CRF question "Will the subject be prescribed Brivaracetam after exiting the EP0077 study?" is "No"). All other patients will be considered as not having an event and will be censored at the date of study termination. For snapshot analyses, patients ongoing in the study will be censored at the date of data cut off.

Change #16

8.2.1 Retention at 3 and 6 months

From:

- Date of study termination < date of first BRV administration + 90 days
- Date of last administration of BRV while in the study < date of first BRV administration + 90 days

Otherwise, patients meeting either condition will be categorized as not having 3 months BRV retention. 90 days is selected because at least 3 months BRV retention is required, hence a patient who attends a month 3 visit early and terminates BRV prior to Day 90, would not be classed as having 3 months retention.

Patients will be classed as having 6 months BRV retention if they do not meet either of the following criteria:

- Date of study termination < date of first BRV administration + 180 days

- Date of last administration of BRV while in the study < date of first BRV administration + 180 days

Otherwise, patients meeting either condition will be categorized as not having 6 months BRV retention. 180 days is selected because at least 6 months BRV retention is required, hence a patient who attends a month 6 visit early and terminates BRV prior to Day 180 would not be classed as having 6 months retention.

BRV Retention at 3 and 6 months will be summarized using the methods described in Section 0 for the FAS only. BRV Retention at 3 and 6 months will be listed as described in Section 8.1.1.

To:

- Date of study termination < date of first BRV administration + 90 days
- Date of last administration of BRV while in the study < date of first BRV administration + 90 days

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 3 months BRV retention. 90 days is selected because at least 3 months BRV retention is required, hence a patient who attends a month 3 visit early and terminates BRV prior to Day 90, would not be classed as having 3 months retention.

Patients will be classed as having 6 months BRV retention if they do not meet either of the following criteria:

- Date of study termination < date of first BRV administration + 180 days
- Date of last administration of BRV while in the study < date of first BRV administration + 180 days

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 6 months BRV retention. 180 days is selected because at least 6 months BRV retention is required, hence a patient who attends a month 6 visit early and terminates BRV prior to Day 180 would not be classed as having 6 months retention.

BRV Retention at 3 and 6 months will be summarized using the methods described in Section 0 for the FAS and the modified FAS. BRV Retention at 3 and 6 months will be listed as described in Section 8.1.1.

Change #17

8.2.2.3 Analysis of seizure frequency related variables

From:

The following tables will be produced on the FAS:

To:

The following tables will be produced on the FAS and all tables except the by subgroup tables will be repeated on the modified FAS:

Change #18

8.2.3 Time to first seizure

From:

The time to first seizure from the date of first dose of BRV for all patients in the FAS will be analyzed using Kaplan-Meier methods, from which the median time to first seizure (and 95% CI) will be calculated, along with 25% and 75% quartiles (and 95% CI for the quartiles). In addition, the cumulative number of events, number at risk, and survival estimate at monthly intervals will be provided. The Kaplan-Meier plot and raw statistical procedure output will be produced for the Kaplan-Meier analysis.

To:

The time to first seizure from the date of first dose of BRV will be analyzed using Kaplan-Meier methods, from which the median time to first seizure (and 95% CI) will be calculated, along with 25% and 75% quartiles (and 95% CI for the quartiles). In addition, the cumulative number of events, number at risk, and survival estimate at monthly intervals will be provided. The Kaplan-Meier plot and raw statistical procedure output will be produced for the Kaplan-Meier analysis. This will be performed on the FAS and the modified FAS.

Change #19

8.3.1.2 Analysis of QOLIE-31-P scores

From:

Descriptive statistics will be presented for QOLIE-31-P: 7 multi-item subscales, the health status item, and total score, and the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal for the FAS). As described in Section 3.2.2, Visit 4 (Month 12/Withdrawal) visits will be mapped to the appropriate scheduled visit and Visit 4 (Month 12) will only include patients completing the study.

The number and percentage of patients in the FAS with clinically meaningful changes in QOLIE-31-P total and subscale scores from Baseline (improvement, no change, or worsening) will be presented for Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal).

To:

All QOLIE-31-P analyses will be performed on the FAS and the modified FAS.

Descriptive statistics will be presented for QOLIE-31-P: 7 multi-item subscales, the health status item, and total score, and the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal). As described in Section 3.2.2, Visit 4 (Month 12/Withdrawal) visits will be mapped to the appropriate scheduled visit and Visit 4 (Month 12) will only include patients completing the study.

The number and percentage of patients with clinically meaningful changes in QOLIE-31-P total and subscale scores from Baseline (improvement, no change, or worsening) will be presented for Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal).

Change #20

8.3.2 EpiTrack

From:

Descriptive statistics will be provided of the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests (after the raw scores have been translated into points). Visit 4 (Month 12/Withdrawal) visits will be mapped to Visit 3 (Month 6) if they are within the windows described in Section 3.2.2. EpiTrack results by visit and the changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12) will also be displayed. The same age correction (age at Visit 1) will be applied at all visits even if a patient changes age category during the study. If a patient is missing any of the raw scores then the subtest and EpiTrack total score will be missing. Change from Baseline will be calculated as:

Post-Baseline point score – Baseline point score.

The number and percentage of patients in the following categories (calculated as described in Section 12.2) will be provided for the FAS:

To:

All EpiTrack analyses will be performed on the FAS and the modified FAS.

Descriptive statistics will be provided of the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests (after the raw scores have been translated into points). Visit 4 (Month 12/Withdrawal) visits will be mapped to Visit 3 (Month 6) if they are within the windows described in Section 3.2.2. EpiTrack results by visit and the changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12) will also be displayed. The same age correction (age at Visit 1) will be applied at all visits even if a patient changes age category during the study. If a patient is missing any of the raw scores then the subtest and EpiTrack total score will be missing. Change from Baseline will be calculated as:

Post-Baseline point score – Baseline point score.

The number and percentage of patients in the following categories (calculated as described in Section 12.2) will be provided:

Change #21

8.3.3 Clinical Global Impression of Change (CGIC) and Patient's Global Impression of Change (PGIC)

From:

The number and percentage of patients with each CGIC and PGIC rating and who had improved, had no change, or worsened at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) will be presented on the FAS. Visit 4 (Month 12/Withdrawal) visits will be mapped as described in Section 3.2.2.

To:

All CGIC and PGIC analyses will be performed on the FAS and the modified FAS. The number and percentage of patients with each CGIC and PGIC rating and who had improved, had no change, or worsened at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) will be presented. Visit 4 (Month 12/Withdrawal) visits will be mapped as described in Section 3.2.2.

Change #22

8.3.4 Change in drug load of AEDs

From:

The total AED drug load at Visit 1 (Baseline), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal), and the change from Baseline will be summarized by descriptive statistics on the FAS. Change from Baseline is defined as: Total AED drug load at Visit 4 (Month 12) or Visit 4 (Month 12/Withdrawal) – total AED drug load at Visit 1 (Baseline).

The number of AEDs (including LEV, VNS use and BRV) taken per patient at Visit 1 (Baseline), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal), and change from Baseline will be summarized by descriptive statistics on the FAS. The number of AEDs at Visit 1 (Baseline) will be equal to the number of AEDs at Study Entry as described in Section 6.4. Patients with VNS use at Visit 1 (Baseline) will be considered to have VNS use during the entire study and as such it will be counted as an AED at Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) as appropriate. The total number of AEDs at a visit is a count of the number of concomitant AEDs, LEV, or BRV that are being taken on the date of the visit with partial dates imputed as described in Section 4.2.2, plus any VNS use. Change from Baseline is defined as: Total number of AEDs at Visit 4 (Month 12) or Visit 4 (Month 12/Withdrawal) – total number of AEDs at Visit 1 (Baseline).

To:

All drug load analyses will be performed on the FAS and the modified FAS.

The total AED drug load at first BRV administration (Baseline), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal), and the change from Baseline will be summarized by descriptive statistics. Change from Baseline is defined as: Total AED drug load at Visit 4 (Month 12) or Visit 4 (Month 12/Withdrawal) – total AED drug load at first BRV administration (Baseline).

The number of AEDs (including LEV, VNS use and BRV) taken per patient at first BRV administration (Baseline), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal), and change from Baseline will be summarized by descriptive statistics. The number of AEDs at first BRV administration (Baseline) will be equal to the number of AEDs at Study Entry as described in Section 6.4. Patients with VNS use at first BRV administration (Baseline) will be considered to have VNS use during the entire study and as such it will be counted as an AED at Visit 4 (Month 12) and Visit 4 (Month 12/Withdrawal) as appropriate. The total number of AEDs at a visit is a count of the number of concomitant AEDs, LEV, or BRV that are being taken on the date of the visit with partial dates imputed as described in Section 4.2.2, plus any VNS use. Change from Baseline is defined as: Total number of AEDs at Visit 4 (Month 12) or Visit 4 (Month 12/Withdrawal) – total number of AEDs at first BRV administration (Baseline).

Change #23

10.1 Extent of exposure

From:

Exposure will be summarized on the SS using descriptive statistics of the continuous variable duration of exposure (days). In addition, the following categories of duration of exposure (days) will show the number of patients with 1 day to <3 months BRV (1-<90 days), 3 months to <6 months BRV (90-<180 days), 6 months to <12 months BRV (180-<330 days), and ≥12 months BRV (≥330 days).

The number and percentage of subjects receiving each daily BRV dose at Day 2, Day 7, Day 14, Day 21, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180 and Day 240 will be summarized in the following BRV dose categories (<= 10mg, >10 to <50mg, >=50mg to <100mg, >=100mg to <150mg, >=150mg to <=200mg and >200mg the following days for all patients in the Safety Set). In addition, the total number of subjects receiving each Dose category at any time on the study will be presented. Day 1 will be equal to the first BRV administration date. Day 2 is considered as the starting dose due to some patients only receiving one dose (afternoon dose only) on Day 1.

Time to BRV maintenance dose will summarized descriptively for all patients in the safety set and will be defined as:

To:

All exposure analyses will be performed on the SS and the modified FAS.

Exposure will be summarized using descriptive statistics of the continuous variable duration of exposure (days). In addition, the following categories of duration of exposure (days) will show the number of patients with 1 day to <3 months BRV (1-<90 days), 3 months to <6 months BRV (90-<180 days), 6 months to <12 months BRV (180-<330 days), and ≥12 months BRV (≥330 days).

The number and percentage of patients receiving each daily BRV dose at Day 2, Day 7, Day 14, Day 21, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180 and Day 240 will be summarized in the following BRV dose categories (<= 10mg, >10 to <50mg, >=50mg to <100mg, >=100mg to <150mg, >=150mg to <=200mg and >200mg). In addition, the total number of patients receiving each Dose category at any time on the study will be presented. Day 1 will be equal to the first BRV administration date. Day 2 is considered as the starting dose due to some patients only receiving 1 dose (afternoon dose only) on Day 1.

Time to BRV maintenance dose will summarized descriptively and will be defined as:

Change #24

10.2 Adverse events

From:

All patients who terminate the study early (recorded as dropouts in the clinical database per the CRF Study Termination [Dropout] page), and have an ADR with action="Drug withdrawn" (recorded in the UCBs Pharmacovigilance database) will be classed as having an event (discontinued BRV due to ADR). All other patients will be censored. Time to discontinuation of BRV due to ADRs will be analyzed on the SS using Kaplan-Meier methods. The median time to discontinuation (days) of BRV due to ADR (and 95% CI) will be presented along with the 25% and 75% quartiles (and 95% CI for the quartiles). The Kaplan-Meier plot and raw statistical procedure output will also be produced for the Kaplan-Meier analysis.

For each of the following event types, frequency tables of incidence based on the SS will be presented.

To:

All patients who have an ADR with action="Drug withdrawn" (recorded in the UCBs Pharmacovigilance database) will be classed as having an event (discontinued BRV due to ADR). All other patients will be censored. Time to discontinuation of BRV due to ADRs will be analyzed on the SS using Kaplan-Meier methods. The median time to discontinuation (days) of BRV due to ADR (and 95% CI) will be presented along with the 25% and 75% quartiles (and 95% CI for the quartiles). The Kaplan-Meier plot and raw statistical procedure output will also be produced for the Kaplan-Meier analysis.

For each of the following event types, frequency tables of incidence based on the SS will be presented. The overview analysis of TEAEs and ADRs will also be repeated on the modified FAS:

Change #25

12.3 Defined Daily Dose (DDD)

From:

AEDs recorded on the study will have their DDD identified using their ATC code and the following website: http://www.whocc.no/atc_ddd_index/

Examples of common AEDs are provided in **Error! Reference source not found.**. Whilst these can be used as a guide all medications (these and any others recorded in the CRF) should be rechecked on the website and the appropriate DDD documented in the ADAM specifications.

Table 12-1: Defined Daily Doses for common AEDs

Compound	ATC code	WHO DDD (mg/day)
Pregabalin	N03AX16	300
Gabapentin	N03AX12	1800
valproic acid	N03AG01	1500

Table 12-1: Defined Daily Doses for common AEDs		
Compound	**ATC code**	**WHO DDD (mg/day)**
Carbamazepine	N03AF01	1000
Lamotrigine	N03AX09	300
Levetiracetam	N03AX14	1500
Oxcarbazepine	N03AF02	1000
Topiramat	N03AX11	300
Clonazepam	N03AE01	8
Primidone	N03AA03	1250
Phenytoin	N03AB02	300
Phenobarbital	N03AA02	100
Zonisamide	N03AX15	200
Lacosamide	N03AX18	300
Eslicarbazepine	N03AF04	800
Tiagabine	N03AG06	30
Clobazam	N05BA09	20
Primidon	N03AA03	1250
Brivaracetam	N03AX23	100
Perampanel	N03AX22	8

To:

AEDs recorded on the study will have their DDD identified using their WHODD preferred term and the following website: http://www.whocc.no/atc_ddd_index/

Examples of common AEDs are provided in **Error! Reference source not found.**. Whilst these can be used as a guide all medications (these and any others recorded in the CRF) should be rechecked on the website and the appropriate DDD documented in the ADAM specifications.

Table 13–1: Defined Daily Doses for common AEDs	
WHODD Preferred Term	**WHO DDD (mg/day)**
Acetazolamide	750
Brivaracetam	100
Carbamazepine	1000
Clobazam	20
Clonazepam	8
Clorazepate Dipotassium	20
Eslicarbazepine	800
Eslicarbazepine Acetate	800
Ethosuximide	1250
Felbamate	2400
Gabapentin	1800
Lacosamide	300
Lamotrigine	300
Levetiracetam	1500
Lorazepam	2.5
Mesuximide	900
Midazolam	15
Midazolam Hydrocholoride	15
Nitrazepam	5
Oxcarbazepine	1000
Perampanel	8
Phenobarbital	100

Table 13–1: Defined Daily Doses for common AEDs	
WHODD Preferred Term	**WHO DDD (mg/day)**
Phenytoin	300
Pregabalin	300
Primidone	1250
Stiripentol	1000
Sultiame	400
Tiagabine	30
Topiramate	300
Valproate	1500
Zonisamide	200

13.4 AMENDMENT 4

Rationale for the amendment

The SAP has been amended to implement any changes to the planned analyses made during the course of the study since approval of the previous version of the SAP. In particular changes resulting from the review of the third interim analysis have been incorporated.

Modifications and changes

Specific changes

Change #1

1 Introduction

From:

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of data collected in EP0077. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity with, the Final Protocol Amendment dated 25-Oct-2018.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly.

The content of this SAP is compatible with the International Conference on Harmonization (ICH)/ Food and Drug Administration (FDA) E9 Guidance documents (ICH E9, 1998).

UCB is the Sponsor and PRA Health Sciences is the contract research organization (CRO) for this study.

To:

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of data collected in EP0077. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity with, the Final Protocol Amendment 1, dated 25-Oct-2018.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly.

The content of this SAP is compatible with the International Conference on Harmonization (ICH)/ Food and Drug Administration (FDA) E9 Guidance documents (ICH E9, 1998).

UCB is the Sponsor and PRA Health Sciences is the contract research organization (CRO) for this study.

Change #2

2.2.2 Secondary variables

From:

The following secondary variables will be measured:

- BRV retention at 3 months
- BRV retention at 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 3 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 12 months (end of Observation Period)
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 3 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 6 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 12 months (end of Observation Period)
- Response based on percent reduction in POS (seizures per 28 days) at 3 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at 6 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at 12 months (end of Observation Period) (response is a reduction of ≥50%)
- Seizure freedom at 3 months
- Seizure freedom at 6 months
- Seizure freedom at 12 months (end of Observation Period)
- Time to first seizure after first dose of BRV

To:

The following secondary variables will be measured:

- BRV retention at 3 months
- BRV retention at 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 3 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 12 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to end of Observation Period

- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 3 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 6 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 12 months
- Percent reduction in POS frequency (seizures per 28 days) from Baseline to end of Observation Period
- Response based on percent reduction in POS (seizures per 28 days) at 3 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at 6 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at 12 months (response is a reduction of ≥50%)
- Response based on percent reduction in POS (seizures per 28 days) at end of Observation Period (response is a reduction of ≥50%)
- Seizure freedom at 3 months
- Seizure freedom at 6 months
- Seizure freedom at 12 months
- Seizure freedom at end of Observation Period
- Time to first seizure after first dose of BRV

Change #3

2.2.3 Other variables

From:

The following other variables will be measured:

- Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) total and subscale scores at 3, 6, and 12 months and change in QOLIE-31-P scores from Baseline to 3, 6, and 12 months (end of observation)
- Presence of clinically meaningful change from Baseline to 3, 6 and 12 months (end of observation) in QOLIE-31-P
- EpiTrack® performance at 6 and 12 months
- EpiTrack change category from Baseline to 6 and 12 months and from 6 months to 12 months
- EpiTrack total score at 6 and 12 months and change from Baseline to 6 and 12 months
- EpiTrack total and individual subtest scores at 12 months and change in EpiTrack scores from Baseline to 12 months

- Clinical Global Impression of Change (CGIC) rating at 3, 6, and 12 months (end of observation)
- Patient's Global Impression of Change (PGIC) rating at 3, 6, and 12 months (end of observation)
- Change in drug load (ie, number of products, daily dose per given product, ratio of dose and Defined Daily Dose [DDD, http://www.whocc.no/atc_ddd_index/], frequency, drug class) of antiepileptic drugs (AEDs) from Baseline to the end of Observation Period

To:

The following other variables will be measured:

- Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) total and subscale scores at 3, 6, and 12 months and change in QOLIE-31-P scores from Baseline to 3, 6, and 12 months and end of Observation Period
- Presence of clinically meaningful change from Baseline to 3, 6 and 12 months and end of Observation Period in QOLIE-31-P
- EpiTrack® performance at 6 and 12 months
- EpiTrack change category from Baseline to 6 and 12 months and from 6 months to 12 months
- EpiTrack total score at 6 and 12 months and change from Baseline to 6 and 12 months
- EpiTrack total and individual subtest scores at 12 months and change in EpiTrack scores from Baseline to 12 months
- Clinical Global Impression of Change (CGIC) rating at 3, 6, and 12 months and end of Observation Period
- Patient's Global Impression of Change (PGIC) rating at 3, 6, and 12 months and end of Observation Period
- Change in drug load (ie, number of products, daily dose per given product, ratio of dose and Defined Daily Dose [DDD, http://www.whocc.no/atc_ddd_index/], frequency, drug class) of antiepileptic drugs (AEDs) from Baseline to 12 months and end of Observation Period

Change #4

2.2.4 Tolerability and safety variables

From:

The following tolerability and safety variables will be analyzed:

- Time to discontinuation of BRV due to adverse drug reactions (ADRs)
- Incidence of ADRs
- Incidence of serious ADRs
- Incidence of ADRs leading to discontinuation of BRV

To:

The following tolerability and safety variables will be analyzed:

- Time to discontinuation of BRV due to adverse drug reactions (ADRs)
- Incidence of treatment-emergent AEs and ADRs
- Incidence of serious treatment-emergent AEs and ADRs
- Incidence of ADRs leading to discontinuation of BRV

Change #5

From:

3.2.3 Date of last administration of BRV

Date of last administration of BRV will be defined as last administration of BRV while in the study as recorded in the Study Termination (Dropout) or (Completed Subject) CRF pages. If the date is partial, then use the imputation of partial end dates rules as described in Section 4.2.2.

For the snapshot analyses described in Section 4.3, patients ongoing in the study will not yet have a date of last administration of BRV recorded. For these patients the date of last administration of BRV will be imputed using the date of the data cut off so that an estimate of the exposure to date can be calculated.

For patients who have completed or withdrawn from the study, if the date of last administration is missing, then the last end date from the BRV Medication CRF page (applying the imputation of partial end dates rules as required) will be used. If that date is also missing then the date of first BRV administration as collected on the First Administration of Drug CRF page will be used. If this start date is partial, use a day of 01 if month and year are present, or 01 January if only year is present. If all of the above are missing, then it is assumed the patient did not take BRV.

To:

3.2.3 Date of first administration of BRV

Date of first administration will be defined as the date of first BRV administration on the "First Administration of Drug" CRF page. If there is no data related to BRV medication (i.e. on the "First Administration of Drug" CRF page, “Brivaracetam Medication” CRF page, or study termination pages) available, then it is assumed the patient did not take BRV, and date of first administration will not be imputed. If the date of first BRV administration is missing on the "First Administration of Drug" CRF page, then the first non-missing date on the “Brivaracetam Medication” CRF page will be used as the first BRV administration date. In case of a partial date, then use the imputation of partial first BRV administration date rules as described in Section 4.2.2.

If the date of first BRV administration is missing on the "First Administration of Drug" CRF page, then the first non-missing date on the “Brivaracetam Medication” CRF page will be used as the first BRV administration date.

Otherwise the Visit 1 date will be used. This means that for example if a patient has a non-missing date for “Date of last administration of medication (Brivaracetam) while in the study” on the study termination page, no dates on the "First Administration of Drug" CRF page, “Brivaracetam Medication” CRF page then the Visit 1 date will be used.

3.2.4 Date of last administration of BRV

Date of last administration of BRV will be defined as last administration of BRV while in the study as recorded in the Study Termination (Dropout) or (Completed Subject) CRF pages. If the date is partial, then use the imputation of partial end dates rules as described in Section 4.2.2.

For the snapshot analyses described in Section 4.3, patients ongoing in the study will not yet have a date of last administration of BRV recorded. For these patients the date of last administration of BRV will be imputed using the date of the data cut off so that an estimate of the exposure to date can be calculated.

For patients who have completed or withdrawn from the study, if the date of last administration is missing, then the last end date from the BRV Medication CRF page (applying the imputation of partial end dates rules as required) will be used. If that date is also missing then the date of first BRV administration as described in Section 3.2.3 will be used. If all of the above are missing, then it is assumed the patient did not take BRV.

Change #6

3.2.5 VNS Use

This section was newly added with the following text:

Patients will be considered to have VNS use if the answer to the CRF question “Has a VNS magnet been used?” is equal to “Yes”.

Change #7

3.4 Protocol deviations

From:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary effectiveness or key safety/tolerability for an individual patient. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific documents. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. In addition, prior to database lock, all important protocol deviations will be reviewed during the data evaluation meeting (DEM), in order to confirm exclusion from the study analysis sets defined in Section 3.5.

To:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary effectiveness or key safety/tolerability for an individual patient. The criteria for identifying important protocol deviations will be defined

within the appropriate protocol-specific documents. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. In addition, prior to CRF lock, all important protocol deviations will be reviewed during the data evaluation meeting (DEM), in order to confirm exclusion from the study analysis sets defined in Section 3.5.

Change #8

3.5 Analysis sets

The last paragraph was updated.

From:

Modified FAS listings to investigate compliance with the approved SmPC will be created and reviewed at the DEM prior to database lock in order to determine which patients will be included in the modified FAS. If the number of patients in the modified FAS is sufficiently different to that in the FAS, then key demographic, effectiveness and safety tables will be repeated on the modified FAS.

To:

Modified FAS listings to investigate compliance with the approved SmPC will be created and reviewed at the DEM prior to database lock in order to determine which patients will be included in the modified FAS. If the number of patients in the modified FAS is sufficiently different to that in the SS, then key demographic, effectiveness and safety tables will be repeated on the modified FAS.

Change #9

3.8 Coding dictionaries

From:

Adverse drug reactions will be coded using version 20.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the September 2017 version of World Health Organization Drug Dictionary (WHODD). Medical history is not being collected for this study and concomitant medical procedures will not be coded.

To:

Adverse drug reactions will be coded using version 23.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the September 2017 version of World Health Organization Drug Dictionary (WHODD). Medical history is not being collected for this study and concomitant medical procedures will not be coded.

Change #10

3.9 Changes to protocol-defined analyses

From:

The time point of the EpiTrack change category variable was corrected to be from "6 months to 12 months" instead of from "6 months to 12 months (end of observation period)". This was to be consistent with all other EpiTrack analyses which include all patients at the same point in time, which in this case is 12 months after BRV administration.

End of observation summaries for the QOLIE, PGIC and CGIC were added, in addition to the protocol defined summaries of Month 12 data for study completers.

Summaries of adverse events were added in addition to summaries of ADRs for regulatory reporting requirements.

To:

A summary of the change from Baseline to 6 months in individual subtest scores was added to be consistent with the analysis of the EpiTrack total score.

According to the protocol seizure freedom at the end of the Observation Period should be presented. However seizure freedom at the end of the Observation Period will not be presented.

Change #11

4.2.2 Times and Dates

From:

Partial dates may be imputed for statistical analyses for specific outcomes according to the following rules. There will be no imputation of missing times. In general, imputed dates will not be shown in listings with the exception of showing imputed dates alongside partial dates for key derivations.

Imputation of partial start dates:

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

Imputation of partial end dates:

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

To:

Partial dates may be imputed for statistical analyses for specific outcomes according to the following rules. There will be no imputation of missing times. In general, imputed dates will not be shown in listings with the exception of showing imputed dates alongside partial dates for key derivations.

Imputation of partial first BRV administration date:

- If the day of first BRV administration is missing and the month and year are the same as the month and year of Visit 1 then the date of Visit 1 will be imputed as the date of first BRV administration. Otherwise impute 1st of the month.
- If the day and the month of first BRV administration are missing then no imputation of the partial date will be done.

Imputation of partial start dates:

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

Imputation of partial end dates:

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

The imputation rules should not create an inconsistency in the data.

Change #12

4.3 Interim analyses and data monitoring

From:

No formal interim analyses are planned; however, 3 nonformal interim analyses (snapshot analyses) will be performed in order to assess early treatment effectiveness, as follows:

- A first snapshot analysis is to be performed with a data cut-off date approximately at the end of 2016 or when 80 patients have completed Visit 2 (Month 3), whichever occurs first. All

patients with available data in the database will be included in the analyses. A subset of the end of study TFLs will be produced.

- A second snapshot analysis is to be performed with a data cut-off date approximately at the end of 2017, depending on recruitment status. If the recruitment schedule results in there not being enough additional data from the previous snapshot then the snapshot cut-off date may be delayed to ensure approximately 200 patients with Visit 2 (Month 3). It is expected that all TFLs identified in the SAP and Mock TFL shells will be delivered including all visits in the database at the time of the snapshot cut off.
- A third snapshot analysis will be performed with a data cut-off date on 28 Nov 2019. All TFLs identified in the SAP and Mock TFL shells will be delivered including all visits in the database at the time of the snapshot cut off.

As data is entered in an ongoing way throughout the study and cleaning is ongoing, data discrepancies in the snapshot analyses are possible. Any data discrepancies observed in the database at the time of the snapshot analyses will be discussed and their impact on the analysis documented.

To:

No formal interim analyses are planned; however, 3 nonformal interim analyses (snapshot analyses) were performed in order to assess early treatment effectiveness, as follows:

- A first snapshot analysis was to be performed with a data cut-off date approximately at the end of 2016 or when 80 patients have completed Visit 2 (Month 3), whichever occurs first. The snapshot was taken on 05 Oct 2016. All patients with available data in the database were included in the analyses. A subset of the end of study TFLs were produced.
- A second snapshot analysis was to be performed with a data cut-off date approximately at the end of 2017, depending on recruitment status. If the recruitment schedule would have resulted in there not being enough additional data from the previous snapshot then the snapshot cut-off date could have been delayed to ensure approximately 200 patients had Visit 2 (Month 3). The snapshot was taken on 13 Apr 2018. All TFLs identified in the SAP and Mock TFL shells at the time of the snapshot were delivered including all visits available in the database at the time of the snapshot cut off.
- A third snapshot analysis was performed with a data cut-off date on 28 Nov 2019. All TFLs identified in the SAP amendment 3 and Mock TFL shells were delivered including all visits in the database at the time of the snapshot cut off.

As data is entered in an ongoing way throughout the study and cleaning is ongoing, data discrepancies in the snapshot analyses are possible. Any data discrepancies observed in the database at the time of the snapshot analyses were discussed and their impact on the analysis documented.

Change #13

4.6 Use of subsets of subjects

From:

All effectiveness analysis will be performed on the FAS and the modified FAS to an estimate of effectiveness for patients using BRV per the approved SmPC.

To:

All effectiveness analysis will be performed on the FAS and the modified FAS to estimate the effectiveness for patients using BRV per the approved SmPC.

In addition, the responder analysis and the seizure freedom analysis will be repeated on the FAS and modified FAS for:

- patients who completed the study
- patients who discontinued the study due to a lack of efficacy

Change #14

4.8 Examination of subgroups

From:

- Age at Visit 1 (<65 and ≥65 years).
- Time since first diagnosis of epilepsy (0-<1 years, 1-<5 years, 5-10 years, >10 years): Defined in Section 6.2
- Number of AEDs at study entry (0, 1, ≥2 AEDs) : Defined in Section 6.4
- Number of Historical AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- Historical Levetiracetam (LEV) use (Yes, No): Defined in Section 6.4
- Number of Lifetime AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- 28-day Baseline all seizures frequency (≤5, >5-10, >10) : Defined in Section 8.2.2.1

The number of patients in the subgroup categories listed above will be examined at the DEM meeting to ensure sufficient patients exist in each category for statistical analysis of the primary and secondary variables by subgroup to offer meaningful analyses. For example, if it is deemed that there are an insufficient number of patients in the ≥65 years age at Visit 1 category, then the age at Visit 1 categories may be amended to use <60 and ≥60 years instead.

To:

- Age at Visit 1 (<65 and ≥65 years).
- Time since first diagnosis of epilepsy (0-<1 years, 1-<5 years, 5-10 years, >10 years): Defined in Section 6.2
- Number of AEDs at study entry (0, 1, 2, 3 and >3 AEDs) : Defined in Section 6.4

- Number of Historical AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- Historical Levetiracetam (LEV) use (Yes, No): Defined in Section 6.4
- Number of Lifetime AEDs (0 or 1 or 2 or 3, 4 or 5 or 6, >6): Defined in Section 6.4
- 28-day Baseline all seizures frequency (≤5, >5-10, >10): Defined in Section 8.2.2.1

The number of patients in the subgroup categories listed above will be examined at the DEM meeting to ensure sufficient patients exist in each category for statistical analysis of the primary and secondary variables by subgroup to offer meaningful analyses. For example, if it is deemed that there are an insufficient number of patients in the ≥65 years age at Visit 1 category, then the age at Visit 1 categories may be amended to use <60 and ≥60 years instead.

Change #15

6.4 Prior and concomitant medications

The first sentence was updated.

From:

Medications classified as AEDs or non AEDs in the CRF will be reviewed during the DEM to ensure correct classification. In addition, historical and concomitant medications will be reviewed to ensure documentation in the correct CRF pages.

To:

Medications will be reviewed during the DEM to ensure correct classification. In addition, historical and concomitant medications will be reviewed to ensure documentation in the correct CRF pages.

Change #16

6.4 Prior and concomitant medications

The second set of bullet points were updated.

From:

- Number of patients with/without a VNS magnet
- Number of patients with historical and LEV use at study entry
- Number of historical AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)
- Number of AEDs at study entry, presented using summary statistics and the following categories (0, 1, and ≥2)
- Number of Lifetime AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)

To:

- Number of patients with/without a VNS magnet
- Number of patients with historical and LEV use at study entry
- Number of historical AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)
- Number of AEDs at study entry, presented using summary statistics and the following categories (0, 1, 2, 3 and >3)
- Number of Lifetime AEDs, presented using summary statistics and the following categories (0, 1, 2, 3, 4, 5, 6, >6 and the subgroup categories 0-3, 4-6 and >6)

Change #17

8.1.1 Retention at 12 months

The reference in the second paragraph was corrected.

From:

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 12 months BRV retention. Date of last administration of BRV will be derived as described in Section 3.2.3. 330 days is used to represent 1 year of treatment in accordance with the visit window instructions given to sites (ie, that the 12 month visit should not be prior to 330 days). This is to prevent classing patients as not having BRV retention when in fact they completed the study within 30 days of the target 360 days.

To:

Otherwise, patients meeting either of the bulleted conditions above will be categorized as not having 12 months BRV retention. Date of last administration of BRV will be derived as described in Section 3.2.4. 330 days is used to represent 1 year of treatment in accordance with the visit window instructions given to sites (ie, that the 12 month visit should not be prior to 330 days). This is to prevent classing patients as not having BRV retention when in fact they completed the study within 30 days of the target 360 days.

Change #18

8.1.2 Sensitivity analysis of the primary variable retention at 12 months

95% CIs were added to the last paragraph.

From:

The 12 month retention analysis described in Section 8.1.1 will be repeated on the modified FAS as a sensitivity analysis to represent the retention of patients who take BRV per the SmPC.

In addition, a Kaplan-Meier analysis of time to discontinuation of BRV or study termination will be provided on the FAS and the modified FAS. Time to discontinuation of BRV or study termination will be calculated as:

Minimum of (Date of last administration of BRV while in the study, Date of study termination) – date of first BRV administration + 1

A patient will be considered as having an event if the patient discontinues from the study (Study Termination [Dropout] CRF page completed) or if the patient is not prescribed Brivaracetam after exiting the study (ie, answer to the CRF question "Will the subject be prescribed Brivaracetam after exiting the EP0077 study?" is "No"). All other patients will be considered as not having an event and will be censored at the date of study termination. For snapshot analyses, patients ongoing in the study will be censored at the date of data cut off.

The median time to event (days) will be presented along with the 25% and 75% quartiles. In addition, the cumulative number of events, number at risk and survival estimate at monthly intervals will be provided. The Kaplan-Meier plot and raw statistical procedure output will be produced for the Kaplan-Meier analysis.

To:

The 12 month retention analysis described in Section 8.1.1 will be repeated on the modified FAS as a sensitivity analysis to represent the retention of patients who take BRV per the SmPC

In addition, a Kaplan-Meier analysis of time to discontinuation of BRV or study termination will be provided on the FAS and the modified FAS. Time to discontinuation of BRV or study termination will be calculated as:

Minimum of (Date of last administration of BRV while in the study, Date of study termination) – date of first BRV administration + 1

A patient will be considered as having an event if the patient discontinues from the study (Study Termination [Dropout] CRF page completed) or if the patient is not prescribed Brivaracetam after exiting the study (ie, answer to the CRF question "Will the subject be prescribed Brivaracetam after exiting the EP0077 study?" is "No"). All other patients will be considered as not having an event and will be censored at the date of study termination. For snapshot analyses, patients ongoing in the study will be censored at the date of data cut off.

The median time to event (days) will be presented along with the 25% and 75% quartiles and 95% CIs. In addition, the cumulative number of events, number at risk and survival estimate at monthly intervals will be provided. The Kaplan-Meier plot and raw statistical procedure output will be produced for the Kaplan-Meier analysis.

Change #19

8.2.2.3 Analysis of seizure frequency related variables

A sensitivity analysis was added after the fifth bullet point. The change to the first list of bullets is shown below.

From:

- Descriptive statistics of the POS frequency at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)

- Descriptive statistics of the absolute reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Descriptive statistics of the absolute reduction in POS frequency (seizures per 28 days) by subgroups described in Section 4.8, from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal).
- Descriptive statistics of the percent reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Number and percentage of responders (≥ 50% reduction) at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Number and percentage with seizure freedom (using the 2 methods described in Table 8–1) at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12)
- Number and percentage with seizure freedom (using discontinuations counted as seizure freedom = no) by subgroups described in Section 4.8, at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12)

To:

- Descriptive statistics of the POS frequency at Visit 1 (Baseline), Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Descriptive statistics of the absolute reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Descriptive statistics of the absolute reduction in POS frequency (seizures per 28 days) by subgroups described in Section 4.8, from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal).
- Descriptive statistics of the percent reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- Number and percentage of responders (≥ 50% reduction) at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12/Withdrawal)
- A sensitivity analysis of the responder analysis will be performed on two subsets of the FAS and modified FAS as defined in Section 4.6 (patients who completed the study and patients who discontinued the study due to lack of efficacy).
- Number and percentage with seizure freedom (using the 2 methods described in Table 8–1) at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12)

  A sensitivity analysis of the seizure freedom analysis will be performed on two subsets of the FAS and modified FAS as defined in Section 4.6 (patients who completed the study and patients who discontinued the study due to lack of efficacy).

- Number and percentage with seizure freedom (using discontinuations counted as seizure freedom = no) by subgroups described in Section 4.8, at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12)

Change #20

8.3.2 EpiTrack

From:

All EpiTrack analyses will be performed on the FAS and the modified FAS.

Descriptive statistics will be provided of the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests (after the raw scores have been translated into points). Visit 4 (Month 12/Withdrawal) visits will be mapped to Visit 3 (Month 6) if they are within the windows described in Section 3.2.2. EpiTrack results by visit and the changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12) will also be displayed. The same age correction (age at Visit 1) will be applied at all visits even if a patient changes age category during the study. If a patient is missing any of the raw scores then the subtest and EpiTrack total score will be missing. Change from Baseline will be calculated as:

Post-Baseline point score – Baseline point score.

The number and percentage of patients in the following categories (calculated as described in Section 12.2) will be provided:

- Point score categories (rated 1-7 for Interference, Numbers, Numbers and letters, and Maze test; 2-7 for Verbal fluency and 3-7 for Inverted digit span)
- Cognitive performance categories (excellent, average, mildly impaired, or significantly impaired) at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 4 (Month 12)
- Significant change categories of cognitive function (improved, unchanged, or worsened) for:
  - Visit 3 (Month 6) compared to Visit 1 (Baseline)
  - Visit 4 (Month 12) compared to the Visit 1 (Baseline)
  - Visit 4 (Month 12) compared to Visit 3 (Month 6).

By-patient listings of EpiTrack 6 subtests raw scores and points; the 6 subtests change from Baseline scores and change from Baseline in points; and the age correction, EpiTrack total score, cognitive performance categories, and significant change evaluation will be provided for the All Subjects Documented set.

To:

All EpiTrack analyses will be performed on the FAS and the modified FAS. EpiTrack score after age correction will be referred to as "EpiTrack total score".

Descriptive statistics will be provided for the EpiTrack total score calculated as described in Section 12.2 and the individual point scores of the 6 subtests. Visit 4 (Month 12/Withdrawal) visits will be mapped to Visit 3 (Month 6) if they are within the windows described in Section 3.2.2. EpiTrack results by visit and the changes from Visit 1 (Baseline) to Visit 3 (Month 6) and

Visit 4 (Month 12) will also be displayed. The same age correction (age at Visit 1) will be applied at all visits even if a patient changes age category during the study. . If any of the individual point scores are outside of the plausible range then they will be set to missing in the tables but will be listed in the listings. If a patient is missing any of the individual point scores or the individual point score is outside of the plausible range then the EpiTrack total score will be missing. Change from Baseline will be calculated as:

Post-Baseline score – Baseline score.

The number and percentage of patients in the following categories (calculated as described in Section 12.2) will be provided:

- Point score categories (rated 1-7 for Interference, Numbers, Numbers and letters, and Maze test; 2-7 for Verbal fluency and 3-7 for Inverted digit span)
- Cognitive performance categories (excellent, average, mildly impaired, or significantly impaired) at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 4 (Month 12)
- Significant change categories of cognitive function (improved, unchanged, or worsened) for:
  - Visit 3 (Month 6) compared to Visit 1 (Baseline)
  - Visit 4 (Month 12) compared to the Visit 1 (Baseline)
  - Visit 4 (Month 12) compared to Visit 3 (Month 6).

By-patient listings of 6 EpiTrack individual subtest scores; the change from Baseline for the 6 individual subtest scores; and the age correction, EpiTrack total score, cognitive performance categories, and significant change evaluation will be provided for the All Subjects Documented set.

Change #21

8.3.4 Change in drug load of AEDs

Text was added to the fourth paragraph.

From:

The drug load per AED at each visit will be added together to give a total AED drug load per visit.

To:

The drug load per AED at each visit will be added together to give a total AED drug load per visit. To avoid an underestimation of the drug load on the first and last visits (on which only 1 of the usual 2 doses may have been recorded), AED drug load at first BRV administration will be calculated for the Day 2 for all patients and the last available record with morning and evening dosage will be used for the Visit 4 drug load analysis.

Change #22

10.1 Extent of exposure

An additional timepoint was added to the sixth paragraph.

From:

The number and percentage of patients receiving each daily BRV dose at Day 2, Day 7, Day 14, Day 21, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180 and Day 240 will be summarized in the following BRV dose categories (<= 10mg, >10 to <50mg, >=50mg to <100mg, >=100mg to <150mg, >=150mg to <=200mg and >200mg). In addition, the total number of patients receiving each Dose category at any time on the study will be presented. Day 1 will be equal to the first BRV administration date. Day 2 is considered as the starting dose due to some patients only receiving 1 dose (afternoon dose only) on Day 1.

To:

The number and percentage of patients receiving each daily BRV dose at Day 2, Day 7, Day 14, Day 21, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180, Day 240 and Day 330 will be summarized in the following BRV dose categories (<= 10mg, >10 to <50mg, >=50mg to <100mg, >=100mg to <150mg, >=150mg to <=200mg and >200mg). In addition, the total number of patients receiving each Dose category at any time on the study will be presented. Day 1 will be equal to the first BRV administration date. Day 2 is considered as the starting dose due to some patients only receiving 1 dose (afternoon dose only) on Day 1.

Change #23

10.1 Extent of exposure

The definition of maintenance dose was changed in the eighth paragraph.

From:

Date of first intake of the highest BRV dose during the study – Date of first BRV administration.

To:

Date of first intake of the BRV dose the patient remained on for the longest time during the treatment period – Date of first BRV administration.

If there is more than one dose which was taken for the equally longest time during the treatment period then the date of the first intake of the latter BRV dose will be used in the above calculation. If the patient has the same BRV dose twice (or more than twice) with a gap of BRV treatment in-between then the durations will not be added together to identify the BRV dose the patient remained on for the longest time; they will be considered separately. Similarly if the patient has the same BRV dose at least twice with another BRV dose in-between then the durations will not be added together; they will be considered separately.

Change #23

10.2 Adverse events

The section was updated to account for a new process and counting of AEs and for consistency of terminology. The first paragraph was also changed to add the explanation of the abbreviation, a second paragraph was added and the third to fifth paragraphs were updated for consistency of terminology.

From:

Adverse events (referred to in this section as clinical AEs) and other safety relevant (OSR) events such as overdose or off label use, will be recorded using UCBs Pharmacovigilance database. A list of MedDRA preferred terms will be reviewed prior to database lock and used to define OSR events.

A treatment-emergent adverse event (TEAE) is defined as a AE occurring on or after the date of first BRV administration.

A treatment-emergent adverse event (TEAE) is defined as a clinical reportable AE occurring on or after the date of first BRV administration.

An ADR is defined as:

- An OSR event with an "as reported causality" as "related" (OSR ADR)
- A clinical AE with an "as reported causality" as "related", "unavailable" or missing (Clinical ADR).

Since an ADR is an AE related to the medication to be investigated (BRV), all reported ADRs (both clinical ADRs and OSR ADRs) are considered treatment-emergent and will be included in the ADR table summaries. Any treatment-emergent OSR events which do not have an "as reported causality" of "related" are classed as OSR non-ADRs.

Patients will be classified further into:

1. Patients with an OSR non-ADR and no clinical ADRs
2. Patients with an OSR non-ADR and at least 1 clinical ADR.

If a patient has more than 1 OSR non-ADR then they will be counted once in the patient count and percentage but with all their OSR non-ADRs in the corresponding event count.

An example for 5 patients is shown below to clarify how this classification will be applied.

Row ID	Patient ID	Clinical AE or OSR event	Relationship	ADR or non-ADR	Category 1= Patients with an OSR non-ADR and no clinical ADRs Category 2=Patients with an OSR non-ADR and at least 1 clinical ADR.
1	[redacted]	OSR event	Unavailable	non-ADR	Category 2. OSR non-ADR (row 1) and at least 1 clinical ADR (row 2). The OSR non-ADR count for this patient is 1 event.
2	[redacted]	Clinical AE	Related	ADR	
3	[redacted]	OSR event	Related	ADR	Category 2. OSR non-ADR (row 5) and at least 1 clinical ADR (row 4). Note row 3 is not classed as an OSR non-ADR as it is related and hence already reported in the tables of ADRs. Row 6 is not relevant to the classification as it is a not related (non-ADR) clinical AE. The OSR non-ADR count for this patient is 1 event.
4	[redacted]	Clinical AE	Related	ADR	
5	[redacted]	OSR event	Unavailable	non-ADR	
6	[redacted]	Clinical AE	Not related	non-ADR	
7	[redacted]	OSR event	Unavailable	non-ADR	Category 1. OSR non-ADR (row 7) and no clinical ADR. Note: row 8 is not an ADR hence the patient has no clinical ADRs. The OSR non-ADR count for this patient is 1 event.
8	[redacted]	Clinical AE	Not related	non-ADR	
9	[redacted]	OSR event	Unavailable	non-ADR	Category 2. OSR non-ADR (row 9) and at least 1 clinical ADR (row 10). The OSR non-ADR count for this patient is 1 event.
10	[redacted]	Clinical AE	Unavailable	ADR	
11	[redacted]	OSR event	Unavailable	non-ADR	Category 1. OSR non-ADR (row 11 and row 13) and no clinical ADR. The OSR
12	[redacted]	Clinical AE	Not related	non-ADR	

13	[redacted]	OSR event	Unavailable	non-ADR	non-ADR count for this patient is 2 events.

In order to investigate the time to discontinuation of BRV due to ADRs, the time to discontinuation of BRV for all patients, will be calculated as:

Date of last administration of BRV while in the study – date of first BRV administration + 1

The date of last administration of BRV while in the study (both for completers and dropouts) and the date of first BRV administration will be taken from the CRF Study Termination (Completed Subject), Study Termination (Dropout), and First Administration of Drug pages. All patients who have an ADR with action="Drug withdrawn" (recorded in the UCBs Pharmacovigilance database) will be classed as having an event (discontinued BRV due to ADR). All other patients will be censored. Time to discontinuation of BRV due to ADRs will be analyzed on the SS using Kaplan-Meier methods. The median time to discontinuation (days) of BRV due to ADR (and 95% CI) will be presented along with the 25% and 75% quartiles (and 95% CI for the quartiles). The Kaplan-Meier plot and raw statistical procedure output will also be produced for the Kaplan-Meier analysis.

For each of the following event types, frequency tables of incidence based on the SS will be presented. The overview analysis of TEAEs and ADRs will also be repeated on the modified FAS:

- Overview of TEAEs (including any TEAE, serious TEAE, patient discontinuations of BRV due to TEAE [derived as any TEAEs with action= "Drug withdrawn"], drug-related TEAE [ADRs], all deaths [AEs leading to death], "OSR non-ADRs and no clinical ADR" and "OSR non-ADRs and at least 1 clinical ADR")
- Overview of ADRs (including any ADR, serious ADR, patient discontinuations of BRV due to ADRs [derived as any ADRs with action= "Drug withdrawn"], and all deaths [ADRs leading to death])
- TEAEs by MedDRA SOC and PT
- ADRs by MedDRA SOC and PT
- Non-serious TEAEs above reporting threshold of 5% of patients by MedDRA SOC and PT
- Non-serious ADRs above reporting threshold of 5% of patients by MedDRA SOC and PT
- TEAEs occurring in at least 5% of patients by MedDRA SOC and PT
- ADRs occurring in at least 5% of patients by MedDRA SOC and PT
- Serious TEAEs by MedDRA SOC and PT
- Serious ADRs by MedDRA SOC and PT
- Serious TEAEs – patient numbers
- Serious ADRs – patient numbers
- ADRs leading to permanent discontinuation of BRV by MedDRA SOC and PT

- TEAEs leading to death by MedDRA SOC and PT
- ADRs leading to death by MedDRA SOC and PT
- TEAEs by maximum relationship by SOC and PT

An AE Glossary (including the SOC, PT and reported term) will be provided. In addition, the following by-patient listings of AEs (including flags for TEAEs, ADRs and OSR events), for the All Subjects Documented set will be presented including the MedDRA SOC and PT, reported term, onset and outcome date, duration, seriousness, death, congenital defect, disability, hospitalization, life threatening, medically important event, outcome, relationship to study medication, and action taken with regards to study medication:

- All AEs (If required, this listing will be repeated for patients aged <18 years only)
- All serious AEs
- All AEs leading to permanent discontinuation of BRV

All deaths (AEs leading to death)

To:

Adverse events and other safety relevant (OSR) information such as overdose or off label use, will be recorded using UCBs Pharmacovigilance database.

The UCB SafetyAdHoc Team will provide an ad hoc listing of the safety data with an additional variable named “Case Classification (All)” that allows identification of the “non-reportable” events. Only events that are identified as "reportable" (ie, where Case Classification (All) variable does not include "Non-Reportable") will be imported into the clinical database (SDTM). A list of MedDRA preferred terms (PTs) will be reviewed prior to database lock and used to identify OSR information. All PTs will be classified as AEs or OSR information. OSR information will not be included in the AE tables and listings, with the exception of the overview table for treatment-emergent adverse events (TEAE, see definition below) and OSR information, and the listing of AEs and OSR information that could not be reconciled.

A treatment-emergent adverse event (TEAE) is defined as an AE occurring on or after the date of first BRV administration.

An ADR is defined as a TEAE with an “as reported causality” as “related”, “unavailable” or missing.

In order to investigate the time to discontinuation of BRV due to ADRs, the time to discontinuation of BRV for all patients, will be calculated as:

Date of last administration of BRV while in the study – date of first BRV administration + 1

The date of last administration of BRV while in the study (both for completers and dropouts) and the date of first BRV administration will be taken from the CRF Study Termination (Completed Subject), Study Termination (Dropout), and First Administration of Drug pages. All patients who have an ADR with action=“Drug withdrawn” (recorded in the UCBs Pharmacovigilance database) will be classed as having an event (discontinued BRV due to an ADR). All other patients will be censored. Time to discontinuation of BRV due to ADRs will be analyzed on the SS using Kaplan-Meier methods. The median time to discontinuation (days) of BRV due to

ADRs (and 95% CI) will be presented along with the 25% and 75% quartiles (and 95% CI for the quartiles). The Kaplan-Meier plot and raw statistical procedure output will also be produced for the Kaplan-Meier analysis.

For each of the following event types, frequency tables of incidence based on the SS will be presented. The overview analysis of TEAEs and ADRs will also be repeated on the modified FAS:

- Overview of TEAEs and OSR information (including categories for any TEAE, serious TEAE, patient discontinuations of BRV due to TEAE [derived as any TEAEs with action= "Drug withdrawn"], drug-related TEAE [ADRs], all deaths [AEs leading to death]), and OSR information
- Overview of ADRs (including categories for any ADR, serious ADR, patient discontinuations of BRV due to ADRs [derived as any ADRs with action= "Drug withdrawn"], and all deaths [ADRs leading to death])
- TEAEs by MedDRA SOC and PT
- ADRs by MedDRA SOC and PT
- Non-serious TEAEs above reporting threshold of 5% of patients by MedDRA SOC and PT
- Non-serious ADRs above reporting threshold of 5% of patients by MedDRA SOC and PT
- TEAEs occurring in at least 5% of patients by MedDRA SOC and PT
- ADRs occurring in at least 5% of patients by MedDRA SOC and PT
- Serious TEAEs by MedDRA SOC and PT
- Serious ADRs by MedDRA SOC and PT
- Serious TEAEs – patient numbers
- Serious ADRs – patient numbers
- ADRs leading to permanent discontinuation of BRV by MedDRA SOC and PT
- TEAEs leading to death by MedDRA SOC and PT
- ADRs leading to death by MedDRA SOC and PT
- TEAEs by maximum relationship by SOC and PT

An AE Glossary (including the SOC, PT and reported term) will be provided separately for AEs and OSR information. In addition, the following by-patient listings for the All Subjects Documented set will be presented including the MedDRA SOC and PT, reported term, onset and outcome date, duration, seriousness, death, congenital defect, disability, hospitalization, life threatening, medically important event, outcome, relationship to study medication, and action taken with regards to study medication:

- All AEs (this listing will be repeated for patients aged <18 years only)
- All serious AEs
- All AEs leading to permanent discontinuation of BRV

- All deaths (AEs leading to death)
- OSR information
- AEs and OSR information that could not be reconciled (ie, AEs/OSR information for patient numbers that do not exist in the clinical database) . This would be an ad hoc listing which will not be produced until after database lock if necessary.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

Approval Signatures

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