NONINTERVENTIONAL STUDY PROTOCOL EP0077

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

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Noninterventional Study Protocol/Amendment number	Date	Type of amendment
Final Noninterventional Study Protocol	04 Nov 2015	Not applicable
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DECLARATION AND SIGNATURE OF TREATING PHYSICIAN

I confirm that I have carefully read and understood this noninterventional study protocol and agree to conduct this study as outlined in this noninterventional study protocol, as well as local laws and requirements.

I will ensure that all physicians and other staff members read and understand all aspects of this noninterventional study protocol.

I have received and have read all study-related information provided to me.

The objectives and content of this noninterventional study protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Treating physician

<Insert name>

_____
Date/Signature

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AED	antiepileptic drug
BRV	brivaracetam
CDMS	clinical data management system
CGIC	Clinical Global Impression of Change
CI	confidence interval
CRO	contract research organization
DDD	Defined Daily Dose
eCRF	electronic Case Report form
FAS	Full Analysis Set
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LEV	levetiracetam
MedDRA®	Medical Dictionary for Regulatory Activities
NIS	noninterventional study
PGIC	Patient's Global Impression of Change
POS	partial-onset seizure(s)
PS	Patient Safety
QoL	quality of life
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Inventory-Form 31
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SS	Safety Set

1 BACKGROUND AND RATIONALE FOR THE STUDY

In the European Union, Briviact® (Nubriveo® in Italy) (brivaracetam [BRV]) has been approved for adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalization in patients 4 years of age and older with epilepsy. Three formulations have been developed for commercial use: film-coated tablets for oral administration (10, 25, 50, 75, and 100mg), an oral solution (10mg/mL), and a solution for intravenous injection (10mg/mL). Brivaracetam film-coated tablets, oral solution, and solution for intravenous injection show the same area under the concentration-time curve, while the maximum plasma concentration is slightly higher after intravenous administration.

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide) is a 2-pyrrolidone derivative and displays a high and selective interaction with a brain-specific binding site, synaptic vesicle protein 2A. This binding site appears to be the major target for its pharmacological activity.

Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of BRV absorption is not affected by food. The pharmacokinetics are dose-proportional from 10mg to 600mg. Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5L/kg, a value that is close to that of total body water. The plasma half-life of BRV is approximately 9 hours; the total plasma clearance in patients was estimated to 3.6L/hour. The main metabolic pathway of BRV is by hydrolysis of the acetamide group by amidase to the corresponding carboxylic acid, while a second pathway is the ω1-hydroxylation mediated by CYP2C19. The combination of these 2 pathways results in the hydroxyacid metabolite. These 3 metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. Brivaracetam is eliminated primarily by oxidative metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in urine within 72 hours after dosing; less than 10% of BRV is excreted unchanged in urine.

The efficacy of BRV for the adjunctive therapy of POS was established in 3 Phase 3 randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies in subjects 16 years of age and older. The daily dose of BRV ranged from 5 to 200mg/day across these studies. All studies had an 8-week Baseline period followed by a 12-week treatment period with no up-titration. A total of 1558 patients received study drug, of which 1099 received BRV. Study enrollment criteria required that patients had uncontrolled POS despite treatment with either 1 or 2 concomitant antiepileptic drugs (AEDs). Patients were required to have at least 8 POS events during the Baseline period. Adjunctive BRV administration at doses of 50mg/day to 200mg/day without titration resulted in statistically significant and clinically relevant reductions in seizure frequency, including seizure freedom. Brivaracetam was effective and well tolerated when started at these therapeutic doses. Low incidences of adverse events (AEs) and low study discontinuation rates due to AEs were also observed with BRV. A recent small, open-label, Phase 3 study evaluating nonpsychotic behavioral AEs in patients receiving levetiracetam (LEV) who switched to BRV showed that, at the end of the 12-week treatment period, 93.1% patients (27/29) who switched to BRV had clinically meaningful reductions in behavioral AEs, which suggest that patients experiencing behavioral AEs associated with LEV may benefit from switching to BRV (Yates et al, 2015).

EP0077 is the first postauthorization observational study of BRV in the real world, and is designed to collect information on the effectiveness in patients with POS who are treated with BRV in clinical practice after the product is marketed in the European Union.

EP0077 is a postmarketing, multinational, multicenter, noninterventional study (NIS) conducted at specialized sites in approximately 10 European countries, with a 12-month Observation Period. Patients will be treated according to usual medical diagnostic procedures and therapy; commercially available BRV will be prescribed according to normal clinical practice and the current Summary of Product Characteristics (SmPC) in Europe for BRV. The prescription of BRV is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients.

The primary objective of this study is to evaluate the effectiveness of BRV by determining the retention over a 12-month period in a real world setting. The secondary objective of this study is to assess seizure control with BRV treatment.

The patient (or legal representative) will be required to provide written data consent for the use of his/her medical data before inclusion in the study.

2 STUDY TYPE

EP0077 is a postmarketing, multinational, multicenter NIS.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary study objective is to evaluate the effectiveness of BRV in patients with epilepsy with POS with or without secondary generalization in daily clinical practice.

3.2 Secondary objective

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

4 STUDY VARIABLES

4.1 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.

4.2 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

4.3 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 end of Observation Period, 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 AEDs from Baseline to 12 months and end of Observation Period

4.4 Other tolerability and safety variables

The following other 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

5 STUDY DESIGN

EP0077 is a postmarketing, multinational, multicenter, prospective 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 SmPC in Europe for BRV (BRV indicated as adjunctive therapy in the treatment of POS with or without secondary generalization in patients 16 years of age and older with epilepsy). It is planned to include 530 patients in the study (see Section 12.4).

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.

All patients (and/or their parents or legal representatives) have to accept in writing that his/her medical data will be used for the evaluation of the study results by signing a study-specific Patient Data Consent form according to local requirements.

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

For patients who discontinue early, the treating physician should collect data as specified for Visit 4 as a Withdrawal Visit. Information on seizures will be collected using patient epilepsy diaries. All data to be collected at Visits 1, 2, 3, and 4 are described in Section 17, Table 17–1.

At those visits, the information collected by the treating physician will include data from any additional visits that the patients may have performed in between.

No formal interim analyses are planned (see Section 12.3).

The management and reporting of AEs will be handled according to international drug safety regulations and UCB procedures.

Documentation of all study assessments is to be performed by the treating physician in the study-specific electronic Case Report form (eCRF). Although the study is noninterventional in nature, every attempt must be made to assess all participating patients in the same way.

6 EXPECTED STUDY DURATION, PLANNED NUMBER OF PATIENTS AND SITES

It is planned to include 530 patients (see Section 12.4).

Approximately 100 sites are planned for participation. The overall expected enrollment period is approximately 3 years, but this may vary in the different countries depending on the respective start of commercial BRV availability.

The Observation Period per patient will be up to 12 months after initiation of BRV treatment.

7 ANTICIPATED REGIONS AND COUNTRIES

The study will be conducted in approximately 10 European countries with possible extension to other countries. The final selection of countries included will be dependent on the timing of the availability of commercial BRV in the different European countries.

8 SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Selection criteria

Before any data are collected for any patient in this NIS, written data consent will be properly executed and documented.

The following selection criteria must be followed for patients entering the NIS:

1. Patient has never been treated with BRV prior to inclusion in this NIS.
2. The decision by the treating physician to prescribe BRV is made independently of the participation in the NIS.
3. A Patient Data Consent form is signed and dated by the patient or by the parent(s) or legal representative.
4. Patient is a male or female ≥16 years of age.
5. Patient has a clinical diagnosis of epilepsy with POS with or without secondary generalization.
6. Patient meets the criteria for treatment with BRV as adjunctive therapy according to the current SmPC in Europe.
7. Patient uses an epilepsy/seizure diary.

8.2 Withdrawal criteria

Patients are free to withdraw from the NIS at any time, without prejudice to their continued care.

Physicians are free to add or withdraw any medication or to withdraw the patient from the study at their own discretion.

If the physician elects to permanently stop BRV treatment, the patient will be withdrawn from the study.

The primary reason for withdrawal from the NIS must be documented in the patient's eCRF. When the primary reason for withdrawal is lack of effectiveness or an AE, both must be reported as described in Section 10.1.8 of the protocol.

9 PRESCRIBED TREATMENT(S)

Patients will be treated with commercially available BRV and with commercially available AEDs, as prescribed by treating physicians, in accordance with current clinical practice.

9.1 Numbering of patients

Each patient will receive a 5-digit number assigned when entering the study that serves as the patient identifier throughout the study.

The patient identification list will be kept by the treating physician. Access to this list may be granted only to members of staff, authorized persons of UCB (or designees), and the competent authorities. The study monitor is also bound to confidentiality. After the end of the study, the identification list will remain with the physician.

10 ASSESSMENT OF SAFETY

For the assessment of safety of BRV, the causal relationship, seriousness, and outcome of AEs will be collected during the Observation Period. It is the task of the treating physician to make a judgment about a causal relationship with the BRV intake.

10.1 Reporting of AEs or other safety relevant information

10.1.1 Definition of AEs

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to BRV.

10.1.2 Other safety relevant information

Other safety relevant information includes the following:

- Off-label use

  This relates to situations where BRV is intentionally used for a medical purpose not in accordance with the authorized product information.

- Misuse

  This refers to situations where BRV is intentionally and inappropriately used not in accordance with the authorized product information.

- Abuse

  This corresponds to the persistent or sporadic, intentional excessive use of BRV, which is accompanied by harmful physical or psychological effects (2010/84/EU Art 1).

- Medication error

  For the purpose of this NIS, medication error refers to any unintentional error in the prescribing, dispensing, or administration of BRV while in the control of the healthcare professional, patient, or consumer.

- Occupational exposure

  This refers to the exposure to BRV (as defined in 2010/84/EU Art 1), as a result of one's professional or nonprofessional occupation.

- Lack of therapeutic effect
- Overdose

  See Section 10.1.6.

- Suspected transmission of an infectious agent via BRV
- Suspected adverse reaction associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of BRV
- Unexpected therapeutic effect

Note: Reports of off-label use, misuse, abuse, medication error, occupational exposure, lack of drug effect, overdose, transmission of infectious agent, falsified medication, or unexpected therapeutic effect should be reported as described in Section 10.1.8 if considered medically important events by the treating physician.

10.1.3 Reporting and description of AEs or other safety relevant information

In order to ensure complete safety data collection, all AEs and other safety relevant information occurring during the study (ie, after signing the Patient Data Consent form), must be reported. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit (eg, underlying or previous concomitant disease).

Signs or symptoms of the condition/disease for which the prescribed treatment is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the treating physician from the patient's history or the Baseline Period.

When recording an AE, the treating physician should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms, signs, or medical procedures. The Adverse Event Report form for NIS and source documents should be consistent.

Details for completion of the Adverse Event Report form for NIS are described in the AE reporting instructions.

10.1.4 Follow up on AEs or other safety relevant information

An AE or safety relevant information should be followed until it has resolved, has a stable sequelae, the treating physician determines that it is no longer clinically significant, or the patient is lost to follow up.

If an AE is still ongoing at the end of the study for a patient, follow up should be provided until resolution/stable level of sequelae, or until the treating physician no longer deems that it is clinically significant, or until the patient is lost to follow up.

10.1.5 Pregnancy

Treating physicians are required to report the pregnancy of a study participant, pregnancy of a study participant's partner, and a study participant who is breastfeeding.

The pregnancy and the outcome (birth, miscarriage, abortion) and the breastfeeding will be documented on the Pregnancy Report and Outcome form provided to the treating physician. The Pregnancy Report and Outcome form will be provided by UCB's local Patient Safety (PS) department in case of reported pregnancy. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the treating physician has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

If the patient is lost to follow up and/or refuses to give information, written documentation of attempts to contact the patient needs to be provided by the treating physician and filed at the site. UCB's local PS department is the primary contact for any questions related to the data collection for the pregnancy, birth and follow up, and breastfeeding.

In cases where the partner of a male patient included in a NIS becomes pregnant, the treating physician or designee is asked to contact the patient to request consent of the partner via the Partner Pregnancy Consent form that should be available in the treating physician's site file. In case of questions about the consent process, the treating physician may contact UCB's local PS department. The treating physician will complete the Pregnancy Report and Outcome form and send it to UCB's local PS department only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's local PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

10.1.6 Overdose of prescribed treatment

Overdose of prescribed treatment refers to the administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information.

Overdose should be reported on the Adverse Event Report form for NIS, independently of whether there is an AE associated with the excessive dosing or not.

10.1.7 Safety signal detection

Reported AEs from this study will be reviewed periodically, together with other safety information received at UCB, to detect as early as possible any safety concern(s) related to the treatment so that treating physicians, clinical study patients, and regulatory authorities will be informed appropriately and as early as possible.

10.1.8 Procedures for reporting AEs or other safety relevant information

The patient will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs, for example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the treating physician should review any self-assessment procedures (eg, epilepsy/seizure diary, questionnaires) employed.

If an AE or other safety relevant information is reported, UCB must be informed within 1 working day of receipt of this information by the site (see contact information for AE reporting listed in the contact information for AE transmission of the NIS protocol). The treating physician must forward to UCB (or its representative) a duly completed Adverse Event Report form for NIS provided by UCB, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

If clarifications on the AE or other safety relevant information are necessary, UCB shall request additional information from the treating physician.

The Adverse Event Report form for NIS and other requested information must be provided in English.

Additional information (eg, autopsy or laboratory reports) received by the treating physician must be provided within 1 working day.

All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Adverse Event Report form for NIS.

The treating physician is specifically requested to collect and report to UCB (or its representative) any AEs or other safety relevant information, and to also inform participating patients of the need to inform the treating physician of any AE or other safety relevant information during the study.

11 ASSESSMENT OF EFFECTIVENESS AND HEALTH-RELATED QUALITY OF LIFE VARIABLES

Retention will be based on the number of patients remaining in the study and on BRV treatment at each study visit.

The treating physician will evaluate at each visit, as part of standard practice with the patient, the frequency and type of seizures experienced by the patient since the previous study visit. Seizure information will be based on the patient diary. Both paper and electronic diaries are acceptable forms. The date and the number (where possible) of epileptic seizures will be recorded on the diary and, if available, undesirable events with start and end dates, and changes in concomitant

medication. The treating physician will review the diary at each study visit and will interview the patient to obtain or clarify any missing or incomplete information.

The QOLIE-31-P Version 2 will be used to evaluate the health-related quality of life (QoL) of study patients (Cramer and Van Hammée, 2003). The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998) that includes 30 items grouped into 7 multi-item subscales (seizure worry [5 items], overall QoL [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 single health status item. The subscale scores, the total score, and the health status item score are calculated according to the scoring algorithm defined in the scoring manual, with scores ranging from 0 to 100 and higher scores indicating better function. In addition to these 31 items, the QOLIE-31-P contains 7 items assessing the degree of "distress" associated with the topic of each sub-scale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

EpiTrack is a tool designed to assess and track changes in cognitive function in people with epilepsy who are treated with AEDs (Witt and Helmstaedter, 2013). This screening tool uses a short list of critical questions and visual indicators to assist healthcare professionals in detecting problems with attention and executive function. It allows for the tracking of the course of cognition in patients with epilepsy in parallel with changes to AED treatment. EpiTrack assesses attention and executive functions through the patient's answers to a combination of verbal and visual tests. This 15-minute screening tool consists of 6 simple subtests and has been validated for use with patients aged 16 to 87 years. Although an age adapted and validated version is available for children and adolescents of 6 to 18 years (EpiTrack Junior), for patients aged 16 to 18 in this NIS it is recommended that the version for adults is used.

The Clinical Global Impression scales (Guy and Bonato, 1970) were initially developed for a risk-benefit estimation within the treatment of mentally ill patients. The 4 global scales (Severity of Illness, Change in Severity from Baseline, Therapeutic Efficacy, and Tolerability of Treatment) are used as different measures of treatment outcome in different kinds of pharmacological studies. The Change in Severity scale (CGIC) is used in this NIS and ranges from 1 (very much improved) to 7 (very much worse).

The PGIC (Hurst and Bolton, 2004) is a 7-point categorical rating scale in which the patient rates the changes in functioning over time from 1 (very much improved) to 7 (very much worse). The PGIC is to be completed during an interview between the patient and the treating physician or designee.

Although there is no direct correlation between the results of the questionnaires/scales and occurrence of AEs, the treating physician should evaluate any significant change for the potential reporting of an AE.

12 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan (SAP).

12.1 Definition of 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. The SS will be used for the analysis of the safety data and Baseline characteristics of the patients.

The Full Analysis Set (FAS) is defined as all patients in the SS who did not receive BRV before entering this NIS. The FAS will be used for the analysis of BRV retention (ie, the primary variable) and the secondary 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 in Europe.

12.2 Planned analyses

All variables will be summarized using descriptive statistics; there will be no inferential analyses. For continuous variables, summary statistics (number of available observations, mean, standard deviation, minimum, median, maximum, 25% and 75% quartiles, and interquartile range) will be tabulated. Categorical variables will be summarized by the number of patients and the percent of patients in each category.

Data from patients who prematurely withdraw from the study will be analyzed up to the final visit attended. Data from patients who withdraw the data consent are used up to the date of withdrawal of consent.

Visit 4 (Month 12/End of Observation Period) will be completed by patients who complete the study (ie, those who complete the Study Termination NIS [Completed Subject] eCRF page) and by those with early study termination (ie, those who complete the Study Termination [Dropout] eCRF page). 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/End of Observation Period): Including all data recorded at Visit 4 (ie, completers and patients who withdraw early)

Subgroup analyses of the more relevant variables will be performed. Further sensitivity analysis may also be performed. Details of these analyses will be described in the SAP.

12.2.1 Analysis of the primary variable

Retention will be summarized for the FAS as the number and percentage of patients remaining in the study and on BRV treatment at Visit 4 (Month 12 or end of Observation period). A 2-sided 95% confidence interval (CI) for the BRV retention will be presented.

The retention analysis 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 may be repeated on the modified FAS.

12.2.2 Analysis of secondary variables

Retention at 3 and 6 months will be summarized using the methodology described for the primary variable.

For seizure frequency variables, Baseline seizure frequency will be based on the previous 3 months to estimate the frequency per 28 days.

The following variables will be summarized using descriptive statistics:

- Absolute and 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 and end of Observation Period)

The following variables will be summarized using number and percentage:

- Responders, defined as a patient experiencing a ≥50% 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 and end of Observation Period)
- Seizure-free status at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of Observation Period)

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 will be calculated, along with 25% and 75% quartiles.

These analyses will be performed on the FAS and may be repeated on the modified FAS.

12.2.3 Analysis of other variables

The following variables will be summarized using descriptive statistics:

- QOLIE-31-P: 7 multi-item subscales, health status item, and total score showing observed results and the change from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of Observation Period)
- Total EpiTrack score and the individual scores of the 6 subtests showing observed results and the change from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12)
- Change in drug load of AEDs from Visit 1 (Baseline) to Visit 4 (Month 12) and Visit 4 (Month 12 and end of Observation Period)

The following variables will be summarized using number and percentage:

- Patients with a clinically meaningful change in QOLIE-31-P from Baseline (improvement, no change, or worsening, based on the minimally important change; Borghs et al, 2012) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of Observation Period)
- Patients in each of the cognitive performance categories using the EpiTrack tool (excellent, average, mildly impaired, or significantly impaired) at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 4 (Month 12)

- Patients in change categories of cognitive function (improved, unchanged, or worsened) between the visits (from Visit 1 [Baseline] to Visit 3 [Month 6] and to Visit 4 [Month 12] and from Visit 3 [Month 6] to Visit 4 [Month 12]) based on the assessments using the EpiTrack tool
- Patients with each CGIC and PGIC rating at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of the Observation Period)
- Patients who improved, had no change, and worsened in CGIC and PGIC

These analyses will be performed on the FAS and may be repeated on the modified FAS.

12.2.4 Analysis of other tolerability and safety variables

Adverse events will be coded for analysis with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®).

An ADR is a response to a prescribed treatment that is noxious and not intended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

Time to discontinuation of BRV due to ADRs, from the date of first dose of BRV, will be analyzed using Kaplan-Meier methods. The median time to discontinuation (days) of BRV will be presented along with the 25% and 75% quartiles.

For each of the following event types, frequency tables with the number of events, the number of patients who experience the event, and the percentage of patients who experience the event will be presented by MedDRA system organ class and preferred term:

- Treatment-emergent AEs and ADRs
- Treatment-emergent AEs and ADRs with an incidence ≥5%
- Serious treatment-emergent AEs and ADRs
- ADRs leading to permanent discontinuation of BRV

These analyses will be performed on the SS and may be repeated on the modified FAS.

12.3 Planned interim analysis and data monitoring

Three nonformal interim analyses (snapshot analyses) are planned in this NIS. 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 second snapshot analysis is to be performed with a data cut-off date approximately at the end of 2017, depending on enrollment status.
- A third snapshot analysis may be performed, if needed.

Details of these snapshot analyses will be described in the SAP.

12.4 Determination of sample size

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

When the sample size is 385, a 2-sided 95.0% 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 in this NIS. Withdrawals will not be replaced.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Monitoring

UCB (or designee) will monitor the study to meet UCB's requirements, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization (CRO) or a contract monitor.

In order to safeguard and assure data quality, a site management plan will be developed that will include details on site monitoring visits, site management by telephone, and source data verification.

A central monitoring approach will be applied so monitoring activities are focused on the areas with the highest potential to impact data quality. Ongoing document review, data review, and analysis are performed remotely by UCB/the CRO to examine the data collected in order to check compliance, identify unusual data patterns, deviations from protocol, or missing or invalid data. On-site monitoring visits will be performed on a for-cause basis.

The treating physician and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The treating physician(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, and regulatory inspection(s). All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc).

13.2 Data handling

13.2.1 Case Report form completion

The treating physician is responsible for prompt reporting of accurate and complete data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the treating physician's review and approval (by means of a password/electronic signature) of the completed eCRF will be reapproved by the treating physician.

The treating physician should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

13.2.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

13.2.3 Patient Enrollment log/Patient Identification Code list

The patient's inclusion will be recorded in the Patient Enrollment log.

The treating physician will keep a Patient Identification Code list. This list remains with the treating physician and is used for unambiguous identification of each patient.

The patient's consent and inclusion in the study must be recorded in the patient's medical record. These data should identify the study and document the dates of the patient's participation.

13.3 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, or unsatisfactory patient inclusion with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the treating physicians/institutions and the regulatory authority(ies) (when applicable) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC and other institutions as per national legislation should also be informed (when applicable) and provided with reason(s) for the termination or suspension by UCB or by the treating physician/institution, as specified by the applicable regulatory requirement(s).

13.4 Archiving and data retention

The treating physician will maintain adequate records for the study, including CRFs, medical records, data consent documents, safety reports, and other pertinent data.

All essential documents are to be retained by the treating physician for at least 5 years after the final study report or first publication of the study results becomes available, whichever comes later. These documents should be retained for a longer period, however, if required by the

applicable regulatory requirement(s). The treating physician will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The treating physician will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in UCB's study master file.

13.5 Audit and inspection

The treating physician will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the included patients have been protected, that included patients (ie, signing consent) are appropriate for the study, and that all data relevant for evaluation of the prescribed treatment have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, IRB/IEC standard operating procedures (when applicable), and applicable regulatory requirements.

The treating physician will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the treating physician will immediately inform UCB (or designee).

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Data consent

Patient's data consent must be obtained and documented in accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining data consent, information should be given in a language and at a level of complexity understandable to the patient in both oral and written form by the treating physician (or designee). Each patient will have the opportunity to discuss the study and its alternatives with the treating physician.

Prior to participation in the study, the written Data Consent form should be signed and personally dated by the patient, and/or his/her legal representative, and by the person who conducted the data consent discussion (treating physician or designee). The patient and/or his/her legal representative must receive a copy of the signed and dated Data Consent form. As part of the consent process, each patient must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Data Consent form is amended during the study, the treating physician (or UCB, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Data Consent form by the IRB/IEC (when applicable) and use of the amended form.

14.2 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC (where applicable), as defined in local regulations.

The treating physician/UCB (or its representative) will ensure that an appropriately constituted IRB/IEC that complies with the applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the

study, the treating physician/UCB (or its representative) will forward copies of the protocol, Data Consent form, treating physician's curriculum vitae (if applicable), and all other patient-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a NIS, the treating physician will have written and dated full approval from the responsible IRB/IEC for the NIS.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active treating physicians in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the treating physician or UCB (or its representative), as specified by the applicable regulatory requirements in each concerned country. Where applicable, treating physicians are to provide UCB (or its representative) with evidence of such IRB/IEC notification.

14.3 Patient privacy

UCB staff (or designee) will affirm and uphold the patient's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the patient number assigned at inclusion into the study.

The treating physician agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the patient's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, electrocardiogram reports, admission/discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports for deaths occurring during the study).

14.4 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, the regulatory authorities, and local institutions (if required), prior to being implemented.

15 STUDY LIMITATIONS

This is an observational study and the analysis of the results will be descriptive in nature.

Recruitment of patients will be carried out by treating physicians at selected sites. The individual start date per country will depend upon the commercial availability of BRV in the respective country. Prescription behavior may be influenced by the market access conditions, which may vary per country. The site selection process shall ensure that representative sites regarding treatment routines in all countries are selected. The potential ability to fulfill the study specific documentation requirements, the fact that BRV is actually available/prescribed at the site, and the quality of the sites will be considered as well.

Study procedures should not interfere with the prescribing behavior of treating physicians or with the individual needs of the patients to assure data collection of standardized, reliable clinical data from Baseline to the end of the Observation Period. Study patients are required to be using

their epilepsy/seizure diary. The treating physicians will review the diary at the study visits to ensure accurate, complete, and homogenous collection of the seizure information in the eCRF, and to look for AEs that require reporting.

Study patients should take BRV as adjunctive treatment, according to the current SmPC. This allows for the use of other AEDs and changes in concomitant AEDs, which may have an influence on the results. Changes in concomitant AEDs will be documented, and pre-existing or newly occurring concomitant diseases, as well as associated concomitant medication, will be recorded. Their possible impact on the course or results of this NIS will be evaluated.

16 PUBLICATION

Publication rights are addressed in the treating physician and/or CRO agreements, as applicable.

17 RECOMMENDED SCHEDULE OF STUDY ASSESSMENTS

Table 17–1: Recommended schedule of study assessments

Assessments	Visit 1[a] Baseline/Day 1 First Day of BRV Treatment	Visit 2 3 Months (Approximately 3 months after Baseline according to routine practice [b])	Visit 3 6 Months (Approximately 6 months after Baseline according to routine practice[b])	Visit 4[c] 12 Months (Approximately 12 months after Baseline according to routine practice[b]) End of Observation/ Withdrawal Visit
Signed data consent	X			
Demographic data (date of birth, gender)	X			
Verification of selection criteria	X			
General epilepsy history[d]	X			
Confirmation of epilepsy syndrome diagnosis	X			
Reason for BRV initiation	X			
Date of BRV initiation	X			
Record BRV daily dose	X	X	X	X
Review patient diary[e]	X	X	X	X
Reason for BRV discontinuation				X
Documentation of seizure information (including seizure date, frequency, and type)[f]	X	X	X	X
Concomitant AEDs[g]	X	X	X	X
Other concomitant epilepsy treatment	X	X	X	X
Other concomitant relevant medications	X	X	X	X

Table 17–1: Recommended schedule of study assessments

Assessments	Visit 1[a] Baseline/Day 1 First Day of BRV Treatment	Visit 2 3 Months (Approximately 3 months after Baseline according to routine practice [b])	Visit 3 6 Months (Approximately 6 months after Baseline according to routine practice[b])	Visit 4[c] 12 Months (Approximately 12 months after Baseline according to routine practice[b]) End of Observation/ Withdrawal Visit
Recording of AEs	X[h]	X	X	X
QOLIE-31-P	X	X	X	X
EpiTrack cognition assessment	X		X	X
CGIC		X	X	X
PGIC		X	X	X
Withdrawal criteria		X	X	
Study termination				X

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; CGIC=Clinical Global Impression of Change; PGIC= Patient's Global Impression of Change; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory-Form 31

[a] Visit 1 will be performed after the decision is taken to start adjunctive BRV therapy. Treatment with BRV should be initiated according to routine clinical practice. If the first dose of BRV is given on the same day as Visit 1, it should be administered after Baseline assessments are complete.

[b] The frequency of visits after Visit 1 will be based on local clinical practice and the patients' requirements. The clinical procedures performed at each visit will also follow local clinical practice.

[c] For patients who discontinue early, the treating physician should collect data as specified for Visit 4 as a Withdrawal Visit.

[d] To include year of first epilepsy diagnosis, lifetime AEDs, etiology. Dates of use of levetiracetam with dosages and reason for discontinuation will be recorded when applicable.

[e] The treating physician will explain the importance of diary completion to the patient and will review his/her diary at each visit.

[f] The treating physician will evaluate at each visit the frequency and type of seizures experienced by the patient since the previous study visit. At Baseline, seizure frequency will be based on the previous 3 months to estimate the frequency per 28 days.

[g] Record name of AED and dose, and any changes after Visit 1.

[h] Adverse events will be recorded from the moment data consent is obtained.

18 REFERENCES

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Witt JA, Helmstaedter C. Monitoring the cognitive effects of antiepileptic pharmacotherapy/approaching the individual patient. Epilepsy Behav. 2013;26(3):450-6.

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19.3 Clinical Global Impression of Change

Clinical Global Impression of Change

Check the box below which describes the subject's condition over the past 4 weeks compared to baseline.

☐$_1$ very much improved

☐$_2$ much improved

☐$_3$ minimally improved

☐$_4$ no change

☐$_5$ minimally worse

☐$_6$ much worse

☐$_7$ very much worse

19.4 Patient's Global Impression of Change

Patient's Global Impression of Change

Over the past 4 weeks, how have you felt compared to before you entered this study? (Please check the number that best describes your condition).

☐$_1$ very much improved

☐$_2$ much improved

☐$_3$ minimally improved

☐$_4$ no change

☐5 minimally worse

☐6 much worse

☐7 very much worse

19.5 NIS Protocol Amendment 1

Rationale for the amendment

The primary purpose of this amendment is to increase the sample size to limit the risk of bias in the statistical analysis for the primary endpoint in this NIS related to the inclusion of a very heterogeneous population of patients with different Baseline characteristics of their disease condition. This is a consequence of a longer enrollment period than initially planned for reaching the targeted sample size. The first 100 patients were all enrolled in Germany in early 2016 and the enrollment in that country was closed, while the opening of other European countries was delayed because of BRV availability in those countries, with enrollment still ongoing. The second interim snapshot performed in Apr 2018 showed great diversity in the patient's characteristics as well as in their medical history, which is fully consistent with known limitations of real-life setting studies and should be addressed properly. The initial assumptions of enrolling 430 patients to obtain 385 patients in the FAS, allowing for approximately 10% of patients to not be included, have not changed, but the enrollment of an additional 100 patients was agreed upon, allowing sensitivity analyses to be performed.

Additional changes have been made in the statistical analysis section to account for changes made to the SAP, including a third planned snapshot analysis and clarification of Visit 4 (Month 12/end of Observation Period) in the analyses. Current approval status of BRV in the European Union has been updated, including the brand name of BRV in Italy, which is the only country where BRV is not marketed as Briviact® but as Nubriveo®. Additional clarifications and administrative changes have also been made.

Modifications and changes

- The sample size has been revised to 530 patients.
- The contact information for AE transmission has been updated by including the participating countries only.
- The brand name for Italy Nubriveo® has been added.
- The approval status of BRV as adjunctive therapy in the treatment of POS with or without secondary generalization in the European Union has been updated to 4 years of age and older.
- The timepoints for the secondary and other study variables have been revised as per the SAP.
- Tolerability and safety variables have been re-named as Other tolerability and safety variables for disclosure purposes.
- Treatment-emergent AEs have been added as other tolerability and safety variables.
- The planned sensitivity analyses of the primary variable have been added.
- Statements regarding the analyses that may be repeated on the modified FAS have been added.
- A third planned snapshot analysis has been added.

Specific changes

Change #1

CONTACT INFORMATION FOR AE TRANSMISSION

Country	Fax number	Email address
Austria	+43 1 291 80 21	DS.at@ucb.com
Baltic region: Estonia, Lithuania, Latvia	+358 10 234 6821	DS-at@ucb.com
Belgium / Luxemburg	+32 2 559 9009	DS.be@ucb.com
Bulgaria	+359 2 961 54 88	DS.bg@ucb.com
Czech Republic	+420 224 829 152	DS.cz@ucb.com
Denmark	+45 32 46 24 01	DS-at@ucb.com
Finland	+358 10 234 6821	DS-at@ucb.com
France	+33 1 4729 4591	pharmacovigilance-fr@ucb.com
Germany	+49 2173 48 2010	DS.de@ucb.com
Greece	+30 210 9974 199	DS.gr@ucb.com
Hungary	+36 1 275 2998	DS.hu@ucb.com
Italy	+39 02 30079 246	DS.it@ucb.com
Netherlands	+31 76 587 5264	DS.nl@ucb.com
Norway	+45 32 46 24 01	DS.Norway@ucb.com
Poland	+48 22 745 23 00	DS.pl@ucb.com
Portugal	+351 21 464 32 29	ds.portugal@ucb.com
Romania	+40 213 112 950	DSRoumania@ucb.com
Slovakia	+420 224 829 152	DS.cz@ucb.com
Spain	+34 91 57 22572	drugsafetyspain@ucb.com
Sweden	+45 32 46 24 01	ds.se-dk@ucb.com
Switzerland	+41 58 822 3181	2ds.ch@ucb.com
United Kingdom	+44 1 753 7858	DS.uk@ucb.com

Has been changed to:

Country	Fax number	Email address
Denmark	+45 32 46 24 01	DS.dk@ucb.com
Germany	+49 2173 48 2010	DS.de@ucb.com

Country	Fax number	Email address
Hungary	+36 1 275 2998	DS.hu@ucb.com
Ireland	+44 1 753 7858	AEReporting@ucb.com
Italy	+39 02 30079 246	DS.it@ucb.com
Netherlands	+31 76 587 5264	DS.nl@ucb.com
Norway	+45 32 46 24 01	DS.Norway@ucb.com
Spain	+34 91 57 22572	drugsafetyspain@ucb.com
United Kingdom	+44 1 753 7858	AEReporting@ucb.com

Change #2

1 BACKGROUND AND RATIONALE FOR THE STUDY

Briviact® (brivaracetam [BRV]) was submitted for Marketing Authorisation Application to the European Medicines Agency as adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalization in patients 16 years of age and older with epilepsy.

Has been changed to:

In the European Union, Briviact® (Nubriveo® in Italy) (brivaracetam [BRV]) has been approved for adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalization in patients 4 years of age and older with epilepsy.

Change #3

4.2 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 (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

Has been changed 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 #4

4.3 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
- Presence of clinically meaningful change from Baseline to 3, 6 and 12 months 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 (end of Observation Period)
- 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
- Patient's Global Impression of Change (PGIC) rating at 3, 6, and 12 months
- 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 AEDs from Baseline to the end of Observation Period

Has been changed 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 end of Observation Period, 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 AEDs from Baseline to 12 months and end of Observation Period

Change #5

4.4 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 ADRs
- Incidence of serious ADRs
- Incidence of ADRs leading to discontinuation of BRV

Has been changed to:

4.4 Other tolerability and safety variables

The following other 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 #6

5 STUDY DESIGN

It is planned to include 430 patients in the study (see Section 12.4).

Has been changed to:

It is planned to include 530 patients in the study (see Section 12.4).

Change #7

6 EXPECTED STUDY DURATION, PLANNED NUMBER OF PATIENTS AND SITES

It is planned to include 430 patients, so that 385 patients are expected to be evaluable, which corresponds to a loss of approximately 10% (see Section 12.4).

Approximately 100 sites are planned for participation. The overall expected recruitment period is approximately 2 years, but this may vary in the different countries depending on the respective start of commercial BRV availability.

Has been changed to:

It is planned to include 530 patients (see Section 12.4).

Approximately 100 sites are planned for participation. The overall expected enrollment period is approximately 3 years, but this may vary in the different countries depending on the respective start of commercial BRV availability.

Change #8

12.1 Definition of analysis sets

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.

Has been changed to:

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 in Europe.

Change #9

12.2 Planned analyses

All variables will be summarized using descriptive statistics; there will be no inferential analyses. For continuous variables, summary statistics (number of available observations, mean, standard deviation, minimum, median, maximum, 25% and 75% quartiles, and interquartile range) will be tabulated. Categorical variables will be summarized by the number of patients and the percent of patients in each category.

Data from patients who prematurely withdraw from the study will be analyzed up to the final visit attended. Data from patients who withdraw the data consent are used up to the date of withdrawal of consent.

Subgroup analyses of the more relevant variables will be performed. Planned subgroup analyses include, but are not limited to: refractoriness, concomitant baseline AEDs, lifetime AEDs, prior exposure to LEV, reason for initiation of BRV. Details of these analyses will be described in the SAP.

Has been changed to:

All variables will be summarized using descriptive statistics; there will be no inferential analyses. For continuous variables, summary statistics (number of available observations, mean, standard deviation, minimum, median, maximum, 25% and 75% quartiles, and interquartile range) will be tabulated. Categorical variables will be summarized by the number of patients and the percent of patients in each category.

Data from patients who prematurely withdraw from the study will be analyzed up to the final visit attended. Data from patients who withdraw the data consent are used up to the date of withdrawal of consent.

Visit 4 (Month 12/End of Observation Period) will be completed by patients who complete the study (ie, those who complete the Study Termination NIS [Completed Subject] eCRF page) and by those with early study termination (ie, those who complete the Study Termination [Dropout] eCRF page). 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/End of Observation Period): Including all data recorded at Visit 4 (ie, completers and patients who withdraw early)

Subgroup analyses of the more relevant variables will be performed. Further sensitivity analysis may also be performed. Details of these analyses will be described in the SAP.

Change #10

12.2.1 Analysis of the primary variable

Additional study information:

The retention analysis 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 may be repeated on the modified FAS.

Change #11

12.2.2 Analysis of secondary variables

The following variables will be summarized using descriptive statistics:

- Absolute and percent reduction in POS frequency (seizures per 28 days) from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12 or end of Observation Period)

The following variables will be summarized using number and percentage:

- Responders, defined as a patient experiencing a ≥50% reduction in POS frequency (seizures per 28 days), from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12 or end of Observation Period)
- Seizure-free status at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12 or end of Observation Period)

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 will be calculated, along with 25% and 75% quartiles.

Has been changed to:

The following variables will be summarized using descriptive statistics:

- Absolute and 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 and end of Observation Period)

The following variables will be summarized using number and percentage:

- Responders, defined as a patient experiencing a ≥50% 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 and end of Observation Period)

- Seizure-free status at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of Observation Period)

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 will be calculated, along with 25% and 75% quartiles.

These analyses will be performed on the FAS and may be repeated on the modified FAS.

Change #12

12.2.3 Analysis of other variables

The following variables will be summarized using descriptive statistics:

- QOLIE-31-P: 7 multi-item subscales, health status item, and total score for the showing observed results and the change from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12 or end of Observation Period)
- Total EpiTrack score and the individual scores of the 6 subtests showing observed results and the change from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12 or end of Observation Period)
- Change in drug load of AEDs from Visit 1 (Baseline) to Visit 4 (Month 12 or end of Observation Period)

The following variables will be summarized using number and percentage:

- Patients with a clinically meaningful change in QOLIE-31-P from Baseline (improvement, no change, or worsening, based on the minimally important change; Borghs et al, 2012) to Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12 or end of Observation Period)
- Patients in each of the cognitive performance categories using the EpiTrack tool (excellent, average, mildly impaired, or significantly impaired) at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 4 (Month 12 or end of Observation Period)
- Patients in change categories of cognitive function (improved, unchanged, or worsened) between the visits (from Visit 1 [Baseline] to Visit 3 [Month 6] and to Visit 4 [Month 12 or end of Observation Period] and from Visit 3 [Month 6] to Visit 4 [Month 12 or end of Observation Period]) based on the assessments using the EpiTrack tool
- Patients with each CGIC and PGIC rating at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12 or end of the Observation Period)
- Patients who improved, had no change, and worsened in CGIC and PGIC

Has been changed to:

The following variables will be summarized using descriptive statistics:

- QOLIE-31-P: 7 multi-item subscales, health status item, and total score for the showing observed results and the change from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of Observation Period)

- Total EpiTrack score and the individual scores of the 6 subtests showing observed results and the change from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 4 (Month 12)
- Change in drug load of AEDs from Visit 1 (Baseline) to Visit 4 (Month 12) and Visit 4 (Month 12 and end of Observation Period)

The following variables will be summarized using number and percentage:

- Patients with a clinically meaningful change in QOLIE-31-P from Baseline (improvement, no change, or worsening, based on the minimally important change; Borghs et al, 2012) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of Observation Period)
- Patients in each of the cognitive performance categories using the EpiTrack tool (excellent, average, mildly impaired, or significantly impaired) at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 4 (Month 12)
- Patients in change categories of cognitive function (improved, unchanged, or worsened) between the visits (from Visit 1 [Baseline] to Visit 3 [Month 6] and to Visit 4 [Month 12] and from Visit 3 [Month 6] to Visit 4 [Month 12]) based on the assessments using the EpiTrack tool
- Patients with each CGIC and PGIC rating at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 12), and Visit 4 (Month 12 and end of the Observation Period)
- Patients who improved, had no change, and worsened in CGIC and PGIC

These analyses will be performed on the FAS and may be repeated on the modified FAS.

Change #13

12.2.4 Analysis of tolerability and safety variables

For each of the following event types, frequency tables with the number of events, the number of patients who experience the event, and the percentage of patients who experience the event will be presented by MedDRA system organ class and preferred term:

- ADRs
- ADRs with an incidence ≥5%
- Serious ADRs
- ADRs leading to permanent discontinuation of BRV

Has been changed to:

12.2.4 Analysis of other tolerability and safety variables

For each of the following event types, frequency tables with the number of events, the number of patients who experience the event, and the percentage of patients who experience the event will be presented by MedDRA system organ class and preferred term:

- Treatment-emergent AEs and ADRs
- Treatment-emergent AEs and ADRs with an incidence ≥5%

- Serious treatment-emergent AEs and ADRs
- ADRs leading to permanent discontinuation of BRV

These analyses will be performed on the SS and may be repeated on the modified FAS.

Change #14

12.3 Planned interim analysis and data monitoring

Two nonformal interim analyses (snapshot analyses) are planned in this NIS. 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 second snapshot analysis is to be performed with a data cut-off date approximately at the end of 2017, depending on recruitment status.

Has been changed to:

Three nonformal interim analyses (snapshot analyses) are planned in this NIS. 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 second snapshot analysis is to be performed with a data cut-off date approximately at the end of 2017, depending on enrollment status.
- A third snapshot analysis may be performed, if needed.

Change #15

12.4 Determination of sample size

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

When the sample size is 385, a 2-sided 95.0% 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.

Has been changed to:

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

When the sample size is 385, a 2-sided 95.0% 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 at non-German sites.

It is, therefore, planned to have 530 patients in this NIS. Withdrawals will not be replaced.

DECLARATIONS AND SIGNATURES

Declarations and signatures of persons responsible for the study

I confirm that I have carefully read and understand this noninterventional study protocol and agree to conduct this noninterventional study as outlined in this protocol.

Approval Signatures

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