# PROTOCOL EP0083 AMENDMENT 4

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

## PHASE 3

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| Protocol Amendment 3 | 01 Feb 2019 | Substantial |
| Protocol Amendment 4 | 10 Jan 2020 | Substantial |



**Confidential Material**

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| | |
|---|---|
| AE | adverse event |
| AED | antiepileptic drug |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| BRV | brivaracetam |
| CDMS | clinical data management system |
| CLcr | creatinine clearance |
| CL/F | plasma clearance |
| CNS | central nervous system |
| CPM | Clinical Project Manager |
| CRO | contract research organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CT | computed tomography |
| CYP | cytochrome P450 |
| DEM | data evaluation meeting |
| DRC | daily record card |
| ECG | electrocardiogram |
| EDC | electronic data capture |
| EDV | Early Discontinuation Visit |
| FAS | Full Analysis Set |
| EEG | electroencephalogram |
| eCRF | electronic Case Report form |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| ID | identification |
| IEC | Independent Ethics Committee |
| ILAE | International League Against Epilepsy |
| IMP | investigational medicinal product |

| | |
|---|---|
| IRB | Institutional Review Board |
| IVRS/IWRS | Interactive Voice Response System/Interactive Web Response System |
| LEV | levetiracetam |
| LTFU | long-term follow-up |
| MAP | managed access program |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| PBO | placebo |
| PDILI | potential drug-induced liver injury |
| PK | pharmacokinetic |
| PK-PPS | Pharmacokinetic Per-Protocol Set |
| PPS | Per-Protocol Set |
| PS | Patient Safety |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SS | Safety Set |
| SV2A | synaptic vesicle protein 2A |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| VNS | vagal nerve stimulation |

# 1 SUMMARY

This is a randomized, double-blind, placebo (PBO)-controlled, multicenter, parallel-group study designed to evaluate the efficacy and safety of adjunctive brivaracetam (BRV) in subjects (≥16 to 80 years of age) with partial seizures. The primary objective is to evaluate the efficacy of BRV compared to PBO as adjunctive treatment in adult and adolescent focal epilepsy subjects with partial seizures not fully controlled despite current treatment with 1 or 2 concomitant antiepileptic drugs (AEDs). Secondary objectives are to assess the safety and tolerability of BRV and to characterize the steady-state pharmacokinetics (PK) of BRV in subjects from ≥16 to 80 years of age.

This study will enroll subjects ≥16 years to 80 years of age with partial seizures with or without secondary generalization. Subjects who are not legal adults will be included only where legally permitted and ethically accepted. Subjects will complete an 8-week prospective Baseline Period, followed by a 12-week Treatment Period. Subjects may be eligible for conversion to a long-term follow-up (LTFU) study or managed access program (MAP) upon completion of the Treatment and Transition Period. There is a 4-week Down-Titration Period followed by a 2-week Study Drug-Free Period for subjects not entering the LTFU study or MAP. If BRV is commercially available upon subject completion of the Treatment and Transition Period, subjects will receive BRV directly without entering the LTFU study or MAP.

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

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

The secondary efficacy variables are as follows:

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

Pharmacokinetic variable is BRV (parent compound only) plasma levels.

Safety variables include incidence of treatment-emergent adverse events (TEAEs), incidence of TEAEs leading to study withdrawal, incidence of treatment-emergent serious adverse events (SAEs), changes in clinical laboratory test parameters (blood chemistry, hematology, urinalysis), electrocardiogram (ECG) parameters and findings, changes in vital signs (SBP, DBP, and pulse rate), changes in body weight, physical and neurological examinations, and mental and psychiatric status.

The planned number of evaluable subjects will be a total of 444 (148 subjects per treatment group) for the primary efficacy analysis. The number of prior LEV use subjects will be limited to 30% of the total study population. It is planned to have those subjects recruited in approximately 95 centers.

# 2 INTRODUCTION

## 2.1 Background and epidemiology of targeted disease

Epilepsy is one of the most common and challenging neurological disorders. It has been estimated that over 50 million people are affected worldwide (Engel and Pedley, 1998; Sander and Shorvon, 1996; Hauser et al, 1993; Loiseau et al, 1990). The prevalence of epilepsy is around 1%. The annual incidence in developed countries is approximately 50 to 70 cases per 100,000. In developing countries, the figure is higher due to more limited obstetric services and the greater likelihood of cerebral infection and trauma. The incidence varies greatly with age, with high rates occurring in childhood, falling to low levels in early adult life, but with a second peak in those aged over 65 years. In many people, particularly children, the condition may remit, although a significant proportion will have epilepsy lifelong. The disease duration is often determined by the underlying cause. Sudden unexpected death, a complication of great concern, occurs in 1 to 5 per 1000 patient years, particularly if the seizure disorder remains uncontrolled. The treatment for epilepsy remains difficult, and there is an ongoing medical need for new AEDs. For a considerable proportion of patients (up to 30%), seizure freedom can still not be reached with currently available AEDs (Nasreddine et al, 2010; Kwan and Brodie, 2001).

Diagnosis of epilepsy is based on the recurrence of seizures. Seizures may be caused by an underlying brain disorder or lesion or due to genetic conditions. Characterization of the epileptic syndrome has profound implications for treatment and prognosis. The major dichotomy for the diagnosis of epilepsy being the differentiation between focal epilepsies (ie, related to a focal brain dysfunction) which are the most frequent and account for approximately 60 to 70% of all cases, and generalized epilepsy syndromes which represent approximately 25 to 30% of all epilepsy syndromes. In about 10% of cases, other specific syndromes are classified or the classification remains uncertain.

For the purpose of this study the seizure type classification will follow the 1981 International League Against Epilepsy (ILAE) classification of epileptic seizures, which speaks of partial seizures, classified as simple partial seizures (no alteration of consciousness), complex partial seizures (with alteration of consciousness), and secondarily generalized seizures and on the other hand defines generalized seizure types, referred to as absence seizures (typical and atypical), myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Apart from myoclonic seizures, consciousness is almost invariably impaired from the onset of the seizure (ILAE, 1981, Appendix 1 [Section 17.1]).

Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAE-publication (ILAE,1989, Appendix 2 [Section 17.2]).

## 2.2 Background information regarding product

Brivaracetam is a chemical relative of the AED LEV (Keppra®/E-Keppra®). Like LEV, BRV displays a high and selective interaction with a novel brain-specific binding site SV2A (synaptic vesicle protein 2A). However, the binding affinity of BRV for SV2A is approximately 10 fold higher. This binding site appears to be the major target for its pharmacological activity. Unlike LEV, BRV also reduces voltage-dependent sodium currents. Brivaracetam also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid- and glycine induced currents. Brivaracetam is extensively metabolized, but seizure protection appears to be associated with the parent compound.

Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of BRV absorption is not affected by food. The PK is dose-proportional (at least 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 8 hours in young healthy male adults. The main metabolic pathway of BRV is by hydrolysis of the acetamide group to the corresponding carboxylic acid, while a second pathway is the ω1-hydroxylation mediated by CYP2C19 (with contributions of several other isoenzymes). The combination of these 2 pathways results in the hydroxyacid terminal metabolite. These metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, with less than 9% as unchanged BRV, is excreted in urine within 72 hours after dosing.

Pharmacokinetic studies in elderly and in subjects with renal impairment showed a similar PK profile of BRV compared to that in healthy subjects while the elimination of the metabolites was markedly slowed down. A PK study in subjects with hepatic impairment showed a 50% increase in exposure to BRV associated with decreased hydroxylation.

Brivaracetam does not impair the efficacy of oral contraceptives containing 30µg ethinylestradiol and 150µg levonorgestrel. Brivaracetam does not induce cytochrome P450 (CYP) 3A4 using midazolam as a marker probe. Brivaracetam has no interaction on lamotrigine and topiramate. Brivaracetam plasma concentration is not increased by gemfibrozil, a selective CYP2C8/9 inhibitor but is increased in a nonclinically relevant manner in Japanese subjects possessing defective CYP2C19 mutations. Brivaracetam clearance is doubled by rifampicin, a potent CYP inducer.

Trough levels of concomitant AEDs were monitored in all efficacy trials. No significant change from Baseline nor dose-related trend was observed for the plasma concentrations of: carbamazepine, lamotrigine, LEV, oxcarbazepine metabolite, phenobarbital, phenytoin, topiramate, valproate, zonisamide. Carbamazepine epoxide was significantly increased from Baseline at all BRV doses greater than 20mg/day, nearly reaching the upper limit of normal (ULN) (3.0µg/mL) at BRV doses of 100 and 150mg/day.

## 2.3 Efficacy with BRV in fixed-dose Phase 2/3 studies in subjects with partial seizures

The efficacy of BRV for adjunctive therapy in partial seizure was established in 3 randomized, double-blind, PBO-controlled, fixed-dose studies (N01252, N01253, and N01358) in subjects ≥16 years of age. Adjunctive BRV administration at doses of 50mg/day to 200mg/day resulted in statistically significant and clinically relevant reductions in seizure frequency. Brivaracetam was well tolerated at these therapeutic doses.

## 2.4 Safety with BRV

In the BRV clinical development program, 3970 subjects have been exposed to BRV (unique exposures) as of 14 Jan 2019.

In Phase 2/3 studies, a favorable safety and tolerability profile has been demonstrated for BRV. The discontinuation rate and the discontinuation rate due to treatment-emergent adverse events (TEAEs) were low and similar to PBO for all studies. The most common adverse drug reactions in subjects with partial seizures were somnolence, sedation, dizziness, fatigue, and nausea/vomiting. The overall incidence of serious adverse events (SAEs) was low and similar to PBO. There were no clinically relevant changes in laboratory values, vital signs or ECG abnormalities.

In addition, the safety of BRV as long-term adjunctive treatment has been evaluated in 5 LTFU studies (N01125, N01379, N01199, N01315, and N01372). The safety profile in the open-label extension studies (up to 8 years) was consistent to that observed in the short-term, PBO-controlled studies.

For additional details on safety and efficacy of BRV, please refer to the Investigator's Brochure (IB).

## 2.5 Study rationale

This adequate and well-controlled study will be performed to provide data confirming the efficacy and safety of BRV as an AED and to support a new drug application in Japan and China for BRV in the indication of adjunctive treatment in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization.

Studies using BRV as adjunctive therapy in partial seizures in adults have shown the results in terms of both efficacy and safety. Well-controlled confirmatory studies N01252, N01253, and N01358 were designed to assess the efficacy and safety of BRV as adjunctive treatment in refractory epilepsy subjects with partial seizures: N01253 assessed BRV doses of 5, 20, and 50mg/day and provided statistically significant and clinically relevant evidence of efficacy of BRV 50mg/day; N01252 assessed BRV doses of 20, 50, and 100mg/day. Although N01252 was not positive for the primary analysis due to predefined sequential testing, it provided supporting evidence for the efficacy of BRV 100mg/day; and N01358 assessed BRV doses of 100 and 200mg/day and provided statistically significant and clinically relevant evidence of efficacy of BRV 100 and 200mg/day.

A Phase 1, PBO-controlled, single and multiple rising dose study in Japanese healthy subjects (N01209), has shown that the disposition of BRV was similar to that in overseas populations. Brivaracetam was well tolerated and displayed linear and dose-proportional PK. No new

observations were made relative to the known safety and tolerability profile of BRV. The main metabolism pathway of BRV is by hydrolysis of the amide function, and a secondary pathway is hydroxylation mediated by the CYP2C19 isoenzyme. In Japanese subjects bearing 2 nonfunctional alleles of the gene coding for the CYP2C19 isoenzyme (namely, *2/*2, *2/*3 or *3/*3; representing 25% of the study population), formation of the inactive hydroxy metabolite was decreased 10-fold but the plasma clearance (CL/F) of BRV was only decreased by 30% (0.70 mL/min/kg compared to 0.99 mL/min/kg in *1/*1 homozygous extensive metabolisers). It was concluded that no BRV dose adaptation is necessary in Japanese subjects compared to overseas populations and in particular no dose reduction is needed for subjects bearing CYP2C19 mutations.

The proposed study is intended to provide evidence of efficacy, safety, and PK for BRV as adjunctive therapy in subjects with partial seizures. Doses of BRV 50 and 200mg/day will be assessed in EP0083.

# 3 STUDY OBJECTIVE(S)

## 3.1 Primary objective

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

## 3.2 Secondary objective

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

# 4 STUDY VARIABLES

## 4.1 Efficacy variable

### 4.1.1 Primary efficacy variable

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

### 4.1.2 Secondary efficacy variables

Secondary efficacy variables are as follows:

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

- Time to $n^{th}$ (n=1, 5, 10) partial seizure during the 12-week Treatment Period

### 4.2 Pharmacokinetic variable

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

### 4.3 Safety variables

#### 4.3.1 Primary safety variables

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

#### 4.3.2 Other safety variables

The other safety variables are as follows:

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

## 5 STUDY DESIGN

### 5.1 Study description

This is a randomized, double-blind, PBO-controlled, multicenter, therapeutic confirmatory study evaluating 2 doses of BRV. The subject population will be subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. Subjects who are not legal adults will be included only where legally permitted and ethically accepted. Subjects will complete an 8-week prospective Baseline Period, followed by a 12-week Treatment Period.

Subjects may be eligible for conversion to a LTFU study or MAP upon completion of the Treatment and Transition Period. There is a 4-week Down-Titration Period followed by a 2-week Study Drug-Free Period for subjects not entering the LTFU study or MAP. If BRV is commercially available upon subject completion of the Treatment and Transition Period, subjects will receive BRV directly without entering the LTFU study or MAP.

A 1:1:1 central randomization (random permuted blocks) stratified for country, LEV use (LEV naïve vs prior LEV use), and number of AEDs previously used but discontinued prior to study entry (≤2 vs >2 AEDs) will be used to ensure the balance across treatment groups (PBO, BRV 50mg/day, BRV 200mg/day) within each combination of stratification levels. Randomization

will not be stratified by study center due to the expected small number of randomized subjects per study center.

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

### 5.1.1 Study duration per subject

The total duration of the study will be up to approximately 26 weeks with a maximum 16-weeks exposure to BRV consisting of the following study periods:

- Baseline Period (8 weeks)
- Treatment Period (12 weeks)
- Down-Titration Period (4 weeks)
- Study Drug-Free Period (2 weeks)
- Transition Period (2 weeks) (required for subjects participating in the LTFU study or MAP)

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

- For the subject who has completed the Treatment Period, the Investigator will decide whether the subject would benefit or not from continuing the treatment with BRV at the end of the Treatment Period (Visit 7). If the investigator decides the subject would benefit from continued BRV treatment and the subject desires to continue treatment, the subject will enter the LTFU study or MAP.
- Prior to entry into LTFU study or MAP, the informed consent, where applicable, should be obtained from the subject at the end of Treatment Period (Visit 7). Subsequently, the subject will go through the Transition Period, and will be dosed in a double-blind manner in order to maintain the blind.
- As a procedure of MAP, the import license of medication for MAP is necessary. The process to obtain the import license starts after patient enrollment and can on occasions take a long time. To avoid a scenario where a subject cannot enter MAP due to the delayed importation of medication, a temporary period for providing BRV will be prepared as the rescue. Once medication for MAP is ready, a subject can start MAP.

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

### 5.1.2 Planned number of subjects and sites

The planned number of evaluable subjects for the primary efficacy analysis will be a total of 444 (148 subjects per treatment group). The number of prior LEV use subjects will be limited to 30% of the total study population as referenced in Section 13.9.

Considering an anticipated screen failure rate of approximately 20%, approximately 555 subjects will be screened. It is planned to have those subjects recruited in approximately 95 sites (50 Japan sites, 20 Southeast Asia sites in countries and regions specified in Section 5.1.3, and 25 China Mainland sites).

### 5.1.3 Anticipated regions and countries

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

## 5.2 Schedule of study assessments

### Table 5–1: Schedule of study assessments

| Assessments | Prospective Baseline Period (8 weeks) | | | Treatment Period (12 weeks) | | | | Early discontinuation | Transition Period (2 weeks)/ Down Titration Period (4 weeks) | Study Drug-Free Period (2 weeks)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | V4 | V5 | V6 | V7 | EDV | V8 | Safety Visit |
| | W -8 | W -4 | W 0 | W 2 | W 4 | W 8 | W 12 | | W 14/W 16 | W 18 |
| Written informed consent | X | | | | | | | | | |
| Subject ID Card dispense | X | | | | | | | | | |
| Eligibility assessment | X[b] | X[b] | X[b] | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical/procedures history | X | | | | | | | | | |
| Epilepsy history | X | | | | | | | | | |
| Lifetime AED history | X | | | | | | | | | |
| Birth control | X | | | | | | | | | |
| Vital signs[c] | X | X | X | X | X | X | X | X | X | X |
| Body weight and height[e] | X | | X | X | X | X | X | X | X | X |
| Physical examination | X | | X | | | | X | X[d] | X | X |
| Neurological examination | X | | X | | | | X | X[d] | X | X |
| Psychiatric and mental status | X | | X | | | | X | X[d] | X | X |
| ECG | X[f] | | | X | X | | X | X[d] | X[k] | X |
| EEG | X[g] | | | | | | | | | |
| CT scan/MRI | X[h] | | | | | | | | | |
| IVRS/IWRS | X | | X | X | X | X | X | X | X | |
| Subject DRC dispensed | X | X | X | X | X | X | X | X[d] | X[o] | |
| Subject DRC returned and reviewed | | X | X | X | X | X | X | X | X | X |
| Seizure counts[i] | | X | X | X | X | X | X | X | X | X |

## Table 5–1: Schedule of study assessments

| Assessments | Prospective Baseline Period (8 weeks) | | | Treatment Period (12 weeks) | | | | Early discontinuation | Transition Period (2 weeks)/ Down Titration Period (4 weeks) | Study Drug-Free Period (2 weeks)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | V4 | V5 | V6 | V7 | EDV | V8 | Safety Visit |
| | W -8 | W -4 | W 0 | W 2 | W 4 | W 8 | W 12 | | W 14/W 16 | W 18 |
| Laboratory safety assessments[j] | X | | X | X | X | X | X | X[d] | X | X |
| Pregnancy test[l] | X | X | X | X | X | X | X | X[d] | X | X |
| BRV plasma level[m] | | | | X | X | X | X | X[d] | X[n] | |
| AE reporting | X | X | X | X | X | X | X | X | X | X |
| C-SSRS | X | X | X | X | X | X | X | X | X | X |
| Medical procedures | X | X | X | X | X | X | X | X | X | X |
| Concomitant AED(s)/VNS settings | X | X | X | X | X | X | X | X | X | X |
| Concomitant non-AED(s) | X | X | X | X | X | X | X | X | X | X |
| IMP dispensing | | | X | X | X | X | X | X[d] | | |
| IMP return/accountability | | | | X | X | X | X | X[d] | X | |
| End of study status | | | | | | | | X | X[k] | X |

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EDV=early discontinuation visit EEG=electroencephalogram; ID=identification card; IMP=investigational medicinal product; IVRS/IWRS=interactive voice response system/interactive web response system; MAP=managed access program; MRI=magnetic resonance imaging; LTFU=long term follow-up; W=week; V=Visit; VNS=vagal nerve stimulation

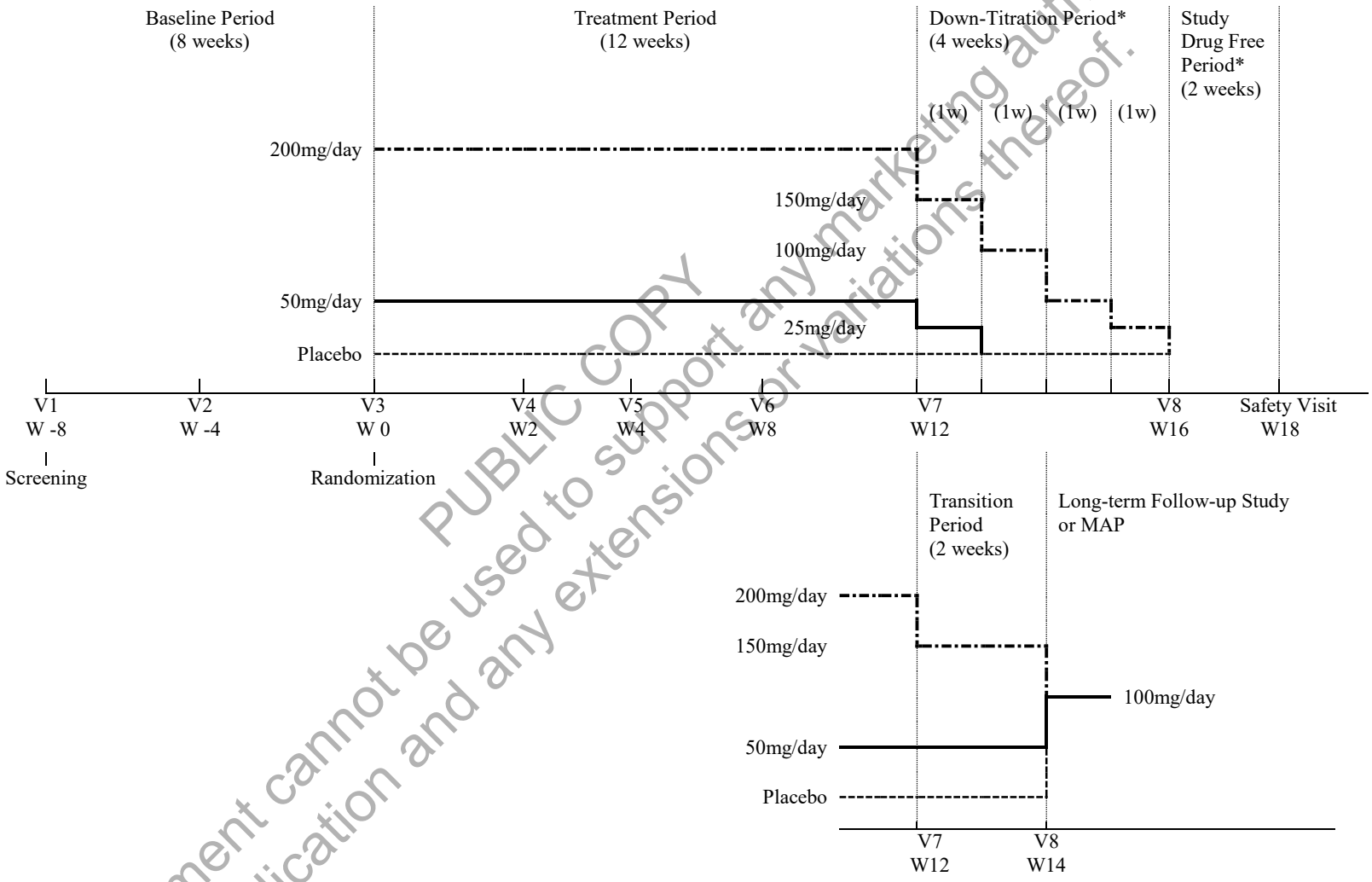
Note: Prior to entry into LTFU or MAP, the informed consent should be obtained from the subject at the end of Treatment Period (Visit 7) (Section 5.1.1).

[a] Safety Visit is not needed for subjects who discontinued before randomization.
[b] Subject is randomized at V3 once all inclusion/exclusion criteria are met.
[c] Vital signs (supine or sitting pulse rate and blood pressure after 5 minutes rest).
[d] Assessment to be conducted in subjects who discontinued after randomization.
[e] Height will be recorded at V1 only.
[f] Baseline ECG has to be scheduled and results received before V3. An ECG at the Safety Visit will be performed only if abnormal at V7/EDV.
[g] Baseline EEG has to be scheduled and results received before V3 if no appropriate EEG available within the last 5 years.
[h] A CT scan or MRI has to be scheduled and results received before V3 if no previous CT scan or MRI available within the last 2 years.
[i] Seizure counts are collected on the subject's DRC on a daily basis.

[j] Laboratory assessment: safety assessment includes hematology, blood chemistry, and urinalysis. Eligibility of subjects will be based on laboratory samples collected at V1. The result of the creatinine clearance will be provided by the central laboratory for all visits and the results at V1 will be used to determine eligibility of the subject.
[k] Only Transition Period
[l] Serum pregnancy at V1 only. Urine pregnancy test will be used at other visits.
[m] Concentrations of BRV will be determined in plasma samples. Date and time of sampling will be recorded. Dosing dates and times for the actual 3 previous BRV doses will be recorded in the eCRF.
[n] At V8, concentrations of BRV will be evaluated only in the Transition Period.
[o] If subjects will not enter to LTFU or MAP, a DRC is dispensed.

## 5.3 Schematic diagram

**Figure 5–1: Schematic diagram**




EDV=early discontinuation visit, V=visit, MAP=managed access program, W=week,
* Subjects with an EDV at any time during the Treatment Period should proceed through the 4-week Down-Titration Period and 2-week Study Drug-Free Period

## 5.4 Rationale for study design and selection of dose

Consistent with the previous fixed dose Phase 3 studies N01253, N01252 and N01358 in EU/US, EP0083 will include an 8-week Baseline Period and a 12-week Treatment Period. The primary efficacy variable is the partial seizure frequency per 28 days during the 12-week Treatment Period.

Brivaracetam 50 to 200mg/day is approved as the effective dose for adults in EU/US. The treatment arms of EP0083 have been decided from the minimum/maximum dose approved.

# 6 SELECTION AND WITHDRAWAL OF SUBJECTS

After the number of prior LEV use subjects are randomized to 30% of the total study population, only LEV naive subjects will be entered in EP0083.

## 6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subjects (male or female) from 16 to 80 years of age at Visit 1, both inclusive. Subjects who are not legal adults may only be included where legally permitted and ethically accepted.
4. Subjects with a body weight ≥40kg during Baseline Period.
5. Female subjects without childbearing potential (postmenopausal for at least 2 years, bilateral oophorectomy or tubal ligation, complete hysterectomy) are eligible. Female subjects with childbearing potential are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least approved dosage of ethinylestradiol per intake in each country where this study is conducted (if subjects is taking any enzyme inducer such as carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort or rifampicin, the dosage of ethinylestradiol should have been modified according to the guidelines for contraceptive treatment in each country), monogamous relationship with vasectomized partner, or barrier contraception are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. Abstinence will be considered as an acceptable method of contraception if the Investigator can document that the subject agrees to be compliant.
6. Well-characterized focal epilepsy/epileptic syndrome according to the 1989 ILAE classification.

7. Presence of an electroencephalogram (EEG) reading compatible with the clinical diagnosis of focal epilepsy within the last 5 years. Baseline EEG has to be scheduled and results received before Visit 3 if no appropriate EEG available within the last 5 years.
8. Presence of a brain magnetic resonance imaging (MRI)/computed tomography (CT) scan performed within the last 2 years. A CT scan or MRI has to be scheduled and results received before Visit 3 if no previous CT scan or MRI available within the last 2 years.
9. Subjects having at least 8 partial seizures (according to the 1981 ILAE classification) during the 8-Week Baseline Period with at least 2 partial seizures during each 4-week interval of the Baseline Period.
10. Subjects having at least 2 partial seizures whether or not secondary generalization per month during the 3 months preceding Visit 1.
11. Subjects uncontrolled while treated by 1 or 2 permitted concomitant AED(s). Vagal Nerve Stimulation (VNS) is allowed and will be counted as a concomitant AED.
12. Permitted concomitant AED(s) and VNS being stable and at optimal dosage for the subject from at least 4 weeks (12 weeks for phenobarbital, phenytoin, and primidone) before Visit 1 and expected to be kept stable during whole study period.

## 6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject previously randomized within this study or any other prior study with BRV as a dosing arm.
2. Simple partial seizure (1981 ILAE classification) nonmotor as only seizure type.
3. Subject has experienced febrile seizures exclusively. The occurrence of febrile seizures in addition to other unprovoked seizures is not exclusionary.
4. Subject has participated in another study of an investigational medication (or a medical device) within the last 30 days or is currently participating in another study of an investigational medication (or a medical device).
5. Subject is currently treated with LEV.
6. Subject has taken LEV within 90 days prior to Visit 1.
7. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.
8. Subject has a known hypersensitivity to any components of the IMP, or any of its excipients.
9. Subject/legal representative not able to read and understand the Informed Consent form, Assent form, or daily record card (DRC) instructions.
10. Subject has severe cognitive impairment or mental retardation as per Investigator assessment
11. Subject whose seizures could not be reliably counted on a regular basis due to their fast and repetitive occurrence (clusters or flurries).

12. Subject has history or presence of status epilepticus during the year preceding Visit 1 or during Baseline.
13. Subject has history or presence of known psychogenic nonepileptic seizures.
14. Subject has taken vigabatrin for 24 weeks prior to Visit 1. Subject with history of vigabatrin use but either no visual fields examination report available including standard static (Humphrey or Octopus) or kinetic perimetry (Goldman) or results of these examinations are abnormal, even though vigabatrin was stopped before 24 weeks.
15. Subject taking any drug with possible central nervous system (CNS) effects except if stable from at least 4 weeks before Visit 1 and expected to be kept stable during whole study period.
16. Subject taking any drug that significantly influences the metabolism of BRV (cytochrome P450 strong inducers such as rifampin/rifampicin) except if the dose has been kept stable at least 4 weeks before Visit 1, and is expected to be kept stable during the Treatment Period.
17. Subject has history of cerebrovascular accident, including transient ischemic attack, in the last 24 weeks.
18. Subject has severe cardiovascular disease or peripheral vascular disease.
19. Subject has presence of any sign (clinical or imaging techniques) suggesting rapidly progressing (ie, not expected to stay stable during study participation) brain disorder or brain tumor. Stable arteriovenous malformations, meningiomas, or other benign tumors may be acceptable.

20a. Subject has any clinical conditions (eg, bone marrow suppression, severe renal impairment with creatinine clearance [CLcr] <30 ml/min/1.73 $m^2$) which impair reliable participation in the study or necessitate the use of medication not allowed by protocol.

21. Subject has chronic hepatic disease.
22. Subject has presence of a terminal illness.
23. Subject has presence of a serious infection.
24. Subject has history of severe adverse hematologic reaction to any drug.
25. Subject has severe disturbance of hemostasis.
26. Subject has >2xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome).

    If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%)

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically

relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

27a. Subject has clinically significant laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results, according to the judgment of the Investigator.

28. Subject has clinically significant ECG abnormalities according to the Investigator.

29. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response (”Yes”) to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1.

30. Subject has known multiple drug allergies or severe drug allergy.

31. Subject is pregnant or lactating.

32. Subject has known alcohol or drug addiction or abuse within the last 2 years.

33. Investigators, co-Investigators, their spouses or children, or any study collaborators. If the Investigator has any other doubts concerning the eligibility, he/she should consult UCB Study Physician or representative for clarification.

## 6.3 Withdrawal criteria

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

Subjects should be withdrawn from the study if any of the following events occur:

- Withdrawal for safety reasons by the Investigator such as a worsening of the seizure profile, eg, occurrence of status epilepticus, seizure clustering, or generalized tonic-clonic seizure, if unknown for the subject
- Subject develops an illness that would interfere with his/her continued participation.
- Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
- Subject takes prohibited concomitant medications as defined in this protocol.
- Subject or legal guardian withdraws his/her consent.
- There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
- The sponsor or a regulatory agency requests withdrawal of the subject.
- Subject has active suicidal ideation without specific plan as indicated by a positive response (“Yes”) to Question 4 of the “Since Last Visit” version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and may be withdrawn from the study based upon the Investigator’s judgment of benefit/risk of continuing the subject in the study/on study medication.

- Subject has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Investigators should attempt to obtain information on subjects in the case of withdrawal. For subjects considered as lost to follow-up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

### 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

# 7 STUDY TREATMENT(S)

## 7.1 Description of investigational medicinal product(s)

Oral film-coated tablets of BRV 25mg, BRV 50mg, and matching PBO tablets will be used in this study.

## 7.2 Treatment(s) to be administered

After an 8-Week Baseline Period and once the subject has fulfilled the eligibility criteria, he/she will be randomized to 50mg/day group, 200mg/day group or PBO group, and enter the double-blind Treatment Period (Visit 3 to Visit 7).

During the Treatment Period, subjects will be treated with BRV 50mg/day, BRV 200mg/day, or the matching PBO tablets in a double-blinded manner. Study medication should be given as 2 equally divided doses administered twice daily except the last week of down-titration. Study medication in the last week of down-titration is given only in the morning. The first intake of newly dispensed study medication should occur in the evening of each visit. Subjects should take IMP according to instructions provided by Investigator.

At the end of the Treatment Period (Visit 7), the subjects entering into the LTFU study or MAP will enter the Transition Period or the subjects not entering into the LTFU study or MAP will enter the Down-Titration Period followed by a Study Drug-Free Period.

The Transition Period (2 weeks) will consist of the following:

- For subjects randomized to BRV 50mg/day group or PBO group, keep same dose as Treatment Period during the Transition Period.
- For subjects randomized to BRV 200mg/day group, the Transition Period will consist of the following: 2 weeks at BRV 150mg/day.

The Down-Titration Period (4 weeks) will consist of the following:

- For subjects randomized to PBO group, keep PBO during the Down-Titration Period.
- For subjects randomized to BRV 50mg/day group, the Down-Titration Period will consist of the following: 1 week at BRV 25mg/day followed by 3 weeks at PBO.
- For subjects randomized to BRV 200mg/day group, the Down-Titration Period will consist of the following: 1 week at BRV 150mg/day, 1 week at BRV 100mg/day, 1 week at BRV 50mg/day, followed by 1 week at BRV 25mg/day.

The down-titration procedure needs to be applied in case of early discontinuation or completion without conversion to the LTFU study or MAP.

## 7.3 Packaging

Brivaracetam tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

## 7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

## 7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator (or designee) is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

## 7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be returned to UCB (or designee) preferably in the original package. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

## 7.7 Procedures for monitoring subject compliance

The IMP (oral tablets) will be supplied to the subject/parent(s)/legal representative(s) at protocol specified time points according to the study schedule of assessments (Table 5–1).

The Investigator will instruct the subject/parent(s)/legal representative(s) to bring back at each visit the kits (even empty) dispensed at the previous visit and containing all the remaining tablets of study medication.

The subjects/parent(s)/legal representative must record the situation of medication compliance every time the subjects take an IMP.

Drug accountability must be done in the subject/parent(s)/legal representative(s) presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

Compliance with investigational product is defined as investigational product consumption by the subject within 80% and 120% of the prescribed dosage. If a subject is found to be persistently noncompliant (<80% or >120%), the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study.

The number of tablets dispensed and returned must be recorded in the source documents.

## 7.8 Concomitant medication(s)/treatment(s)

For any treatment other than the IMP, including over-the-counter products, an accurate record must be kept in the source documents and in the eCRF.

All concomitant medications should be recorded in the eCRF at the Screening Visit and subsequently be recorded only if there is a change regarding the administration of the medication. For all subjects, new medications should be recorded in the eCRF at only the first visit at which they are reported and subsequently only if there is a change. For any change, the start date corresponding to the date of change in administration should be recorded in the eCRF.

For all subjects, all changes in concomitant AEDs and non-AEDs will be recorded on the AED or non-AED concomitant medication page, respectively, in the eCRF. This record should include the name of the drug (preferably the brand name), the dose, the date(s) of administration, formulation(s), and the indication for use.

### 7.8.1 Permitted concomitant treatments (medications and therapies)

All subjects will take 1 or 2 concomitant AEDs (Appendix 3 [Section 17.3]). Only oral-daily use is permitted (any other use or route of administration is prohibited, except when it is used as rescue medication).

All concomitant AEDs except the ones specified in Section 7.8.2 are permitted during the study. All AEDs need to be at a stable dose for at least 4 weeks prior to Visit 1 and kept stable over the whole study period.

If the subject discontinues from the study, the above limitation is not required after the Early discontinuation Visit (EDV), considering subject safety.

Drugs with no CNS effects, which are not strong enzyme inducers/inhibitors, are allowed.

Vagal nerve stimulation is allowed and will be counted as a concomitant AED.

### 7.8.2 Prohibited concomitant treatments (medication and therapies)

The following concomitant medications/treatments are prohibited during the study:

- LEV
- BRV (other than IMP)
- Potassium bromide, sodium bromide, and calcium bromide
- Other investigational products and drugs and medical devices that have not been approved in each country
- Brain surgery (including surgery for examination purposes).

### 7.8.3 Restricted concomitant treatments (medications and therapies)

The following concomitant medications/treatments are restricted during the study:

- Drugs with possible CNS effects (anxiolytics, hypnotic, and neuropsychiatric agents) including benzodiazepines are allowed if at stable dose from at least 4 weeks prior to Visit 1 and during the entire study period. In case of as-needed use, it is allowed the frequency is up to once a week in this study. However, it is prohibited to take more than once a week in this study. Any drug where the route of administration is not oral, except when it is used as rescue medication.
- Any drug that significantly influences the metabolism of BRV (cytochrome P450 strong inducers such as rifampin/rifampicin) are allowed if at stable dose from at least 4 weeks prior to Visit 1 and during the entire study period.

### 7.8.4 Rescue medication

The rescue medication(s) which the dosage form is suppository, injection, and enema preparation are permitted during the study for sudden aggravation or cluster seizures and if the subject's condition requires rescue medication(s) during minor surgical procedures in a relatively short time. In addition, the use of anticonvulsants is permitted as rescue medication. The use of rescue medication is permitted only once a week for a maximum of 4 weeks to control seizures; if the frequency exceeds once a week, the subject will be discontinued from the study.Prior

## 7.9 LEV use

Levetiracetam use within 90 days prior to Visit 1 [(Week -8) Baseline] is prohibited. If a subject has been treated with LEV in the past, in order to participate in the study:

- oral LEV must be discontinued ≥91 days prior to Visit 1, or
- intravenous (iv) LEV must have been administered ≥91 days prior to Visit 1.

The management of LEV cap is specified in Section 13.9.

## 7.10 Blinding

Brivaracetam and matching placebo and their accompanying packaging will be identical in appearance (size and color), so that neither the investigator nor the subject is able to tell whether the subject is receiving BRV or placebo.

At UCB Clinical Trial Supply, kit numbers will be allocated according to the package list generated by a validated program by UCB. This list will be provided to the IVRS/IWRS.

The treatment randomization schedule will be generated by UCB (or designee) in a manner that will ensure that the study team remains blinded, in accordance with current Standard Operating Procedures (SOPs). The randomization schedule will be maintained in a secure location until the study is unblinded for the final statistical analysis.

All sponsor, Investigator sites, and contract research organization (CRO) staff involved with the study will be blinded to the treatment code with the following exceptions:

- Sponsor personnel and its subcontractors directly involved in the packaging of the IMP or in the management of the IVRS/IWRS.

- Sponsor Patient Safety (PS) staff will receive separate access to the IVRS/IWRS in order to meet their requirements for SAE reporting to regulatory authorities.
- Central laboratory staff assaying study drug. However, no randomization list will be provided.

### 7.10.1 Procedures for maintaining and breaking the treatment blind

#### 7.10.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the IVRS/IWRS.

#### 7.10.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IVRS/IWRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The Clinical Project Manager (CPM) or designee will be informed immediately via the IVRS/IWRS when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

## 7.11 Randomization and numbering of subjects

A 1:1:1 central randomization (random permuted blocks) will be stratified for the following to ensure the balance across treatment groups (PBO, BRV 50mg/day, BRV 200mg/day) within each combination of stratification levels.

- Country
- LEV use (LEV naïve vs prior LEV use)
- Number of prior AEDs (≤2/>2) based on AEDs previously used and discontinued prior to Visit 1.

An IVRS/IWRS will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IVRS/IWRS vendor. The IVRS/IWRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the Investigator or designee will contact the IVRS/IWRS and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IVRS/IWRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IVRS/IWRS.

To randomize a subject (Visit 3), the Investigator or designee will contact the IVRS/IWRS and provide brief details about the subject to be randomized. The IVRS/IWRS will automatically inform the Investigator or designee of the subject's randomization number. The IVRS/IWRS will

allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the eCRF.

# 8 STUDY PROCEDURES BY VISIT

The informed consent procedure, as described in Section 14.1, must be completed prior to initiating any other study-specific activities.

A ±3 day window for each specified Visit/Week is allowed, provided the subject has adequate IMP to sustain the visit window.

## 8.1 Visit 1 (Week -8) Baseline

Visit 1 assessments are as follows:

- Written informed consent
- Subject identification (ID) Card dispense
- Eligibility assessment (verification of inclusion and exclusion criteria)
- Demography
- Medical/procedures history
- Epilepsy history
- Lifetime AED history
- Birth control
- Vital signs (blood pressure and pulse rate)
- Body weight and height
- Physical examination
- Neurological examination
- Psychiatric and mental status
- ECG (Baseline ECG has to be done to ensure results received before Visit 3)
- EEG (to be performed before Visit 3 if no previous report available within last 5 years)
- CT scan/MRI (to be performed before Visit 3 if no previous report available within last 2 years)
- IVRS/ IWRS
- Subject DRC dispensed
- Laboratory safety assessments
- Pregnancy test (serum)
- AE reporting
- C-SSRS

- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)

## 8.2 Visit 2 (Week -4)

Visit 2 assessments are as follows:

- Eligibility assessment (verification of inclusion and exclusion criteria)
- Vital signs
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Pregnancy test (urine)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)

## 8.3 Visit 3 (Week 0) Randomization

Visit 3 assessments are as follows:

- Eligibility assessment (verification of inclusion and exclusion criteria)
- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- IVRS/IWRS
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)
- AE reporting

- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)
- IMP dispensing

## 8.4 Visits 4 and 5 (Weeks 2 and 4)

Visit 4 and 5 assessments are the same and as follows:

- Vital signs
- Body weight
- ECG
- IVRS/IWRS
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)
- BRV plasma level
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)
- Concomitant non-AED(s)/VNS settings
- IMP dispensing
- IMP return/accountability

## 8.5 Visit 6 (Week 8)

Visit 6 assessments are as follows:

- Vital signs
- Body weight
- IWRS/IVRS
- Subject DRC dispensed
- Subject DRC returned and reviewed

- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)
- BRV plasma level
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)
- IMP dispensing
- IMP return/accountability

## 8.6 Visit 7 (Week 12)

Visit 7 assessments are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- ECG
- IVRS/IWRS
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)
- BRV plasma level
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)

- IMP dispensing
- IMP return/accountability

Prior to entry into LTFU or MAP, the informed consent should be obtained from the subject.

## 8.7 Early Discontinuation Visit (before randomization)

Assessments for subjects who are discontinued from the study before randomization as follows:

- IVRS/IWRS
- Subject DRC returned and reviewed
- AE reporting
- End of study status

*As for the other assessments, these are not required but still recommended to complete if possible:*

- Vital signs
- Body weight
- Seizure counts
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)

## 8.8 Early Discontinuation Visit (after randomization)

Assessments for subjects that discontinue the study early are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- ECG
- IVRS/IWRS
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)

- BRV plasma level
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)
- IMP dispensing
- IMP return/accountability

## 8.9 Visit 8 (Transition Period)

Assessments for the Transition Period are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- ECG
- IVRS/IWRS
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)
- BRV plasma level
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)
- IMP return/accountability
- End of study status

### 8.9.1 Visit 8 (Down-Titration Period)

Assessments during the Down-Titration Visit are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- IVRS/IWRS
- Subject DRC dispensed
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments
- Pregnancy test (urine)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)
- IMP return/accountability

## 8.10 Safety Visit (Study Drug-Free Period)

Assessments for the Safety Follow-Up Visit are as follows:

(Safety Visit is not needed for subjects that discontinued before randomization)

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Psychiatric and mental status
- ECG (to be performed only if abnormal at Visit 7/EDV)
- Subject DRC returned and reviewed
- Seizure counts
- Laboratory safety assessments

- Pregnancy test (urine)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AED(s)/VNS settings
- Concomitant non-AED(s)
- End of study status

## 8.11 Unscheduled Visit (if applicable)

At any time, the subject may have an additional study visit if the Investigator or the subject and/or legal representative deem it necessary. All information, including reason for visit, any information on AEs, etc, should be collected in the source documents and recorded in the appropriate sections of the eCRF.

If an Unscheduled Visit is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

## 8.12 Handling of biological samples

The safety samples (hematology, biochemistry, urinalysis, and serum pregnancy test) will be routinely assayed and the results sent by fax to the Investigator as specified in Section 11.2.

The central lab will keep plasma samples for BRV plasma level determinations in freezers at -20°C until assayed as well as 1 plasma back-up sample until database lock. These back-up samples can only be destroyed following written authorization from the Clinical Project Manager. Results will only be communicated to the Investigator and study team after database lock.

Methods for collecting, processing, storing, and shipping laboratory samples for determination of BRV plasma levels are described in Section 11.2.

# 9 ASSESSMENT OF EFFICACY

At each visit the subject will receive a DRC with assistance of the parent(s) or legal representative when needed, to be filled in daily for each occurrence of events and to be returned at the next visit. At Visit 8, a DRC will be dispensed for the subjects not willing to enter the LTFU study or MAP. No DRC will be dispensed at the Safety Visit.

The date, the symptom and the number of epileptic seizures will be recorded on the DRC, as well as individual description of seizures, intake of concomitant IMPs, undesirable events with start and end dates, and changes in concomitant medication, if applicable.

The written information will be discussed with the subject at each visit in order to ensure completeness and accuracy. As a result of the discussion, the Investigator will assess the seizures according to the ILAE codes and record the seizure types and frequency on the DRC and eCRF;

he/she will also confirm the presence of AEs (if applicable). The concomitant medication changes, and AEs will be reported by the Investigator on the specific pages of the eCRF

At Visit 3, the 2 DRCs from Baseline must be reviewed for seizure data to confirm that the subject meets eligibility criteria before randomization.

The subject should be educated to complete the DRC (eg, when taking evening tablets). Substantial noncompliance with DRC (seizures recording) may result in subject discontinuation from the study at any time by the Investigator or the Sponsor. The copy of DRC will be retained by Sponsor.

## 9.1 Additional efficacy assessments

### 9.1.1 Medical procedures

From Visit 1 onwards, data on medical procedures (surgery, therapeutic and/or diagnostic) undertaken during the study will be collected and recorded in the eCRF. Electrocardiograms specific to this study will not be recorded on the medical procedures page of the eCRF, but in the modules specifically designed for this purpose. Electroencephalogram and brain CT scan (or MRI where legally required) performed before randomization in order to meet inclusion criteria will be recorded in the modules specifically designed for this purpose.

# 10 ASSESSMENT OF PHARMACOKINETICS

Plasma concentrations of BRV will be determined. Methods for collecting, processing, storing, and shipping laboratory samples for determination of BRV plasma are described in Section 11.2.

# 11 ASSESSMENT OF SAFETY

## 11.1 Adverse events

### 11.1.1 Definitions

#### 11.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP 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 Investigator from the subject's history or the Baseline Period.

#### 11.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

#### 11.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. The procedure for reporting AEs of special interest is the same as that for reporting SAEs (Section 11.1.2.3).

The following are AEs of special interest:

- autoimmune nephritis

- nephritis
- nephritis allergic
- tubulointerstitial nephritis
- uveitis syndrome
- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

### 11.1.2 Procedures for reporting and recording adverse events

The subject 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 Investigator should review any self-assessment procedures (eg, DRC) employed in the study.

#### 11.1.2.1 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, DRC) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

#### 11.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

#### 11.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) 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.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English, with the exception of Japanese reports.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. 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 Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

### 11.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 11.2.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

### 11.1.4 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an EDV.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the EDV.

- A Safety Visit should be scheduled 2 weeks after the subject has discontinued her IMP.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. 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 Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/ CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

### 11.1.5 Suspected transmission of an infectious agent via a medicinal product

A suspected transmission of infectious agent is defined as any infection that is temporally related to the administration of the medicinal product with no other likely cause. The medical monitor should be contacted immediately. No further medicinal product from that specific batch should be administered. Infections should be treated according to normal clinical practice.

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

### 11.1.6 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

### 11.1.7 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

## 11.2 Laboratory measurements

Laboratory assessments will be conducted using standard methods at a central laboratory with the exception of urine pregnancy tests (which will be performed at the unit by clinical study personnel). The central laboratory will provide the Investigator with dedicated, standardized sampling equipment (labels, needles, tubes), and a study-specific laboratory manual, which will explain how to use the equipment and how to ship the samples to the central laboratory.

The total blood volume drawn for clinical laboratory assessments will be a maximum of 10.5mL by sampling, which includes 2mL for hematology, 2.5mL for blood chemistry, and 6mL for BRV plasma level measurements.

The subject must be preferably fasting, but study medication intake must not be delayed. The following safety laboratory parameters will be measured:

**Table 11–1: Laboratory measurements**

| Hematology | Biochemistry | Urinalysis | Pregnancy |
|---|---|---|---|
| WBC | Glucose | Glucose | β-hCG urine/ serum |
| RBC | Sodium | Ketones | |
| Hemoglobin | Potassium | Occult blood | |
| Hematocrit | Calcium | Protein | |
| MCV | Chloride | Nitrites | |
| MCH | Bicarbonate | Leukocytes | |
| MCHC | Phosphorus (inorganic) | Microscopic examination[b] | |
| Platelet count | Total protein | | |
| Lymphocytes (number, %) | Albumin | | |
| Monocytes (number, %) | Total bilirubin[a] | | |
| Neutrophils (number, %) | ALP[a] | | |
| Eosinophils (number, %) | AST (SGOT)[a] | | |
| Basophils (number, %) | ALT (SGPT)[a] | | |
| | GGT[a] | | |
| | Uric acid | | |
| | Urea | | |
| | Creatinine | | |
| | Triglycerides | | |
| | Cholesterol | | |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; GGT=gamma-glutamyltransferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; WBC=white blood cell

[a] This assessment is used for hepatic monitoring.
[b] Includes bacteria, cells, casts, and crystals for all samples.

The CLcr will be calculated over time by the central laboratory using their current methods.

The subject's age, body weight, and gender must be recorded on the laboratory requisition form.

The result of the calculated CLcr will be provided by the central laboratory for all assessments. The results of all safety assessments obtained from the blood sample collected at Visit 1 will be used to determine the eligibility of the subject.

Laboratory safety assessments will be performed at timepoints specified in the schedule of study assessments (Table 5–1). The decision for the treatment at Visit 3 will be based on the results of the laboratory safety sample analysis obtained at Visit 1.

Where applicable females of childbearing potential, a blood pregnancy test (beta-human chorionic gonadotropin [β-hCG] level) or urine pregnancy test will be included in the laboratory safety assessments. If pregnancy is suspected at any time during the study, an interim test should be performed. Results for hematology, biochemistry, urinalysis, and serum pregnancy tests will be provided by fax to the Investigator within 72 hours after sample receipt.

**BRV Plasma Levels**

For BRV plasma levels, the date and time of the last 3 actual intakes will be recorded in the source documentation and eCRF.

One blood sample per visit should be obtained for BRV plasma levels at Visit 4, Visit 5, Visit 6, Visit7, and Visit 8 (Transition Period) or EDV. The Investigator should attempt as far as practically feasible to collect the sample at different times postdose in order to cover the 0 to 12 hour dosing interval (for example, between 0 to 2 hours postdose, 2 to 4 hours postdose, 4 to 8 hours postdose, and 8 to 12 hours postdose).

Brivaracetam plasma levels will be assayed in batch runs. Results of BRV plasma level measurements will only be communicated to the Investigator and UCB study team after database lock.

### 11.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.1.1.3), and, if applicable, also reported as an SAE (see Section 11.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the

2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

Table 11–2 summarizes the approach to investigate PDILI.

## Table 11–2: Required investigations and follow-up for PDILI

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |
| ≥3xULN | ≥2xULN[b] | NA | Hepatology consult.[c]<br>Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP. | Immediate, permanent IMP discontinuation. | Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.3); recommended to occur at the site with HCP. | Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d] |
| ≥3xULN | NA | Yes | | Immediate, temporary or permanent, IMP discontinuation. | | |
| ≥5xULN (and ≥2x Baseline) | <2xULN | No | Discussion with Medical Monitor required.<br>Hepatology consult required if ALT/AST ≥8xULN | Immediate IMP discontinuation | Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.2.1.3). | |

## Table 11–2: Required investigations and follow-up for PDILI

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |
| ≥3xULN (and ≥2x Baseline) and <5xULN | <2xULN | No | Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met. | • Further investigation – immediate IMP discontinuation not required (see Section 11.2.1.2).<br>IMP discontinuation required if any of the following occur:<br>• Subject cannot comply with monitoring schedule.<br>• Liver chemistry values continue to increase.<br>• Liver chemistry values remain ≥3xULN (and ≥2xBaseline) after 2 week monitoring without stabilization or evidence of resolution. | Not required unless otherwise medically indicated (at discretion of Investigator | Monitoring of liver chemistry values at least twice per week for 2 weeks[d]<br>Immediate IMP discontinuation required if:<br>• liver chemistry values continue to increase.<br>After 2 weeks of monitoring liver chemistry values:<br>• Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without stabilization or evidence of resolution<br>Continue to monitor until values normalize, stabilize, or return to within Baseline values[d] |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

#### 11.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the Investigator must discuss the case with the Medical Monitor as soon as possible. If required, the Investigator must also discuss the case with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.2.1.3) and SAE report (if applicable).

#### 11.2.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11–2 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

#### 11.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–3 (laboratory measurements) and Table 11–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

**Table 11–3: PDILI laboratory measurements**

| | |
|---|---|
| **Virology-related** | Hepatitis A IgM antibody |
| | HBsAg |
| | Hepatitis E IgM antibody |
| | HBcAb-IgM |
| | Hepatitis C RNA |
| | Cytomegalovirus IgM antibody |
| | Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing) |
| **Immunology** | Anti-nuclear antibody (qualitative and quantitative) |
| | Anti-smooth muscle antibody (qualitative and quantitative) |
| | Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative) |
| **Hematology** | Eosinophil count |
| **Urinalysis** | Toxicology screen |
| **Chemistry** | Amylase |
| | If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin |
| | Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation |
| **Additional** | Prothrombin time/INR[a] |
| | Serum pregnancy test |
| | PK sample |

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

**Table 11–4: PDILI information to be collected**

| New or updated information |
|---|
| Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included. |
| Pertinent medical history, including the following:<br>• History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease")<br>• Adverse reactions to drugs<br>• Allergies<br>• Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)<br>• Recent travel<br>• Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.) |
| The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash) |
| Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function |
| Alcohol and illicit drug use |
| Results of liver imaging or liver biopsy, if done |
| Results of any specialist or hepatology consult, if done |
| Any postmortem/pathology reports |

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

#### 11.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 11–2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

## 11.3 Other safety measurements

### 11.3.1 ECG

A standard 12-lead ECG will be performed at time points specified in the schedule of study assessments (Table 5–1).

Baseline (Visit 1) results must be received before Visit 3 randomization. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

The original ECG tracing will be signed or initialed and dated by the Investigator and will be retained as part of the source data.

### 11.3.2 Vital signs

Vital signs, including measurements of blood pressure and supine or sitting pulse rate will be performed after 5 minutes of rest at time points specified in the schedule of study assessments (Table 5–1).

The vital signs measurements will be repeated after 30 minutes if unusual values were observed at the initial reading.

### 11.3.3 Physical examinations

A standard physical examination will be performed at time points specified in the schedule of study assessments (Table 5–1). Clinically significant new or worsened abnormalities will have to be reported as AEs.

### 11.3.4 Neurological examination

A standard neurological examination will be performed at time points specified in the schedule of study assessments (Table 5–1). Clinically significant new or worsened abnormalities will have to be reported as AEs.

### 11.3.5 Psychiatric and mental status

Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairment, and behavioral problems at time points specified in the schedule of study assessments (Table 5–1). Clinically significant new or worsened abnormalities will have to be reported as AEs.

### 11.3.6 Body weight and height

At all visits, body weight (subject wearing light clothing without shoes) will be measured. Subjects with a body weight ≥40kg during Baseline Period will be eligible. Height will be recorded at Baseline (Visit 1) only.

### 11.3.7 Neuro-imaging procedure

A brain MRI, brain CT scan should be performed during the Baseline Period if no previous report is available within the last 2 years.

### 11.3.8 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for Baseline/Selection as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed at time points specified in the schedule of study assessments (Table 5–1).

# 12 STUDY MANAGEMENT AND ADMINISTRATION

## 12.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

## 12.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring SOPs, ICH-GCP guideline, 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 CRO or a contract monitor.

The Investigator 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 Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

### 12.2.1 Definition of source data

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). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of CRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Original laboratory results, ECGs, and EEGs are considered as source documents and should be stored with the subject's study information.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records as applicable, such as Holter monitor records or EEG records, must be saved and stored as instructed by UCB (or designee).

### 12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

## 12.3 Data handling

### 12.3.1 Case Report form completion

This study will be performed using electronic data capture (EDC).

The Investigator is responsible for prompt reporting of accurate, complete, and legible 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 Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

### 12.3.2 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. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRF once and are subsequently verified if the study is performed using EDC.

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.

### 12.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

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

## 12.4 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, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory

requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

## 12.5 Archiving and data retention

The record retainer at the study site and the IRB/IEC will retain the GCP defined essential document until at least 10 years after the discontinuation or completion of the study conduct. If UCB requires retention of these documents for longer period, the duration and method of retention will be decided upon discussion between UCB and study site.

It is responsibility of UCB (or designee) to inform the record retainer as to when the documents should no longer to be retained.

## 12.6 Audit and inspection

The Investigator or head of the participating study site 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 subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

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

## 12.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

# 13 STATISTICS

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

## 13.1 Definition of analysis sets

Analysis populations will be defined as follows:

The Safety Set (SS) will include all randomized subjects who will take at least 1 dose of study medication.

The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of study medication and have at least 1 post-Baseline seizure DRC data.

The Per-Protocol Set (PPS) will consist of all subjects in the FAS who do not have a major protocol deviation impacting the primary efficacy variable.

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

All efficacy analyses will primarily be carried out using the FAS. In order to verify the robustness of the efficacy results, the primary efficacy variable will also be analyzed using the PPS. Safety analyses will be carried out using the SS.

All analyses will be based on randomized treatment assignment. Incorrectly treated subjects will be evaluated during the blinded data evaluation meeting (DEM) to assess the potential impact of such cases and any special analysis considerations.

## 13.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation (SD), median, 25th percentile, 75$^{th}$ percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. All statistical testing will be carried out at a 2-sided 0.05 significance level unless otherwise indicated.

Statistical outliers are defined as values that are discordant with other values and are clinically implausible. Exclusion of outliers from an analysis requires thorough justification based on statistical and clinical grounds. Any outliers will be reviewed during the blinded DEMs (see Section 13.5).

## 13.3 Planned efficacy analyses

### 13.3.1 Analysis of the primary efficacy variable

The primary analysis will be based on ANCOVA with log-transformed [log(x+1)] Treatment Period adjusted partial seizure frequency per 28 days as the outcome and effects for treatment group and stratification effects and log-transformed Baseline partial seizure frequency as a continuous covariate, where log represents the natural logarithm function. Seizure frequency within each study period will be standardized to a 28-day duration. Treatment effects will be characterized using percent reduction over PBO based on back-transformation of least squares means. A non-parametric analysis will be carried out to assess the robustness of the parametric ANCOVA results.

This study is stratified by country, LEV use (LEV naïve vs prior LEV use), and number of previously used AEDs (≤2 vs >2). Some combinations of stratification levels may have few subjects. The general rules for pooling stratification levels for statistical analyses will be provided in the SAP, with finalization of any pooling during the blinded DEM.

Statistical testing will be based on the comparison of each BRV treatment group (BRV 50mg/day and 200mg/day) to PBO with control of overall Type I error rate based on the Hochberg procedure. The Hochberg procedure does not require a pre-specified order of testing for BRV dose groups vs PBO. In a setting with a comparison of 2 active groups to PBO, the Hochberg procedure is applied by first testing the BRV group with the larger p-value at the 0.05 level. If statistical significance is achieved at this step, then the study is positive and both BRV dose groups are declared statistically different from PBO. If the largest p-value is not significant at the 0.05 level, then the Hochberg procedure steps to the smaller p-value and tests at the 0.025 level.

If statistical significance is achieved at this step, then the study is positive and the BRV dose group associated with the smaller p-value is declared statistically different from PBO. If the smaller p-value is not significant at the 0.025 level, then neither BRV group is statistically different from PBO and the study is not positive.

### 13.3.2 Analyses of secondary efficacy variables

The secondary efficacy variables will be analyzed with statistical testing at the nominal 0.05 level without adjusting multiplicities.

For treatment and stratification effects, 50% responder rate will be analyzed using a logistic regression with effects for treatment and stratification effects and log-transformed Baseline partial seizure frequency per 28 days as a continuous covariate.

With regard to stratification, the same rule with the Section 13.3.1 will be applied.

Median percent reduction in partial seizure frequency per 28 days from Baseline to the Treatment Period will be compared between each BRV group and PBO using a Wilcoxon-Mann-Whitney test. Hodges Lehmann non-parametric effect estimates and corresponding 95% confidence intervals will be provided. Categorized percent reduction (<-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%) in partial seizure frequency from Baseline to the Treatment Period will be summarized descriptively with comparisons between each BRV group and PBO carried out using a Mantel-Haenszel test for comparison of row mean scores. Seizure freedom rates will be compared between each BRV group and PBO using Fisher's Exact Test. To be considered seizure-free, a subject must not report seizures of any type and must complete the Treatment Period without any missing seizure DRC days.

All seizure frequency (partial, generalized, and unclassified epileptic seizure) per 28 days over the Treatment Period will be analyzed in a manner similar to the primary ANCOVA analysis.

Time to $n^{th}$ (n=1, 5, 10) partial seizure will be compared between each BRV group and PBO using a semi-parametric proportional hazards model with an effect for treatment and log-transformed Baseline partial seizure frequency as a continuous covariate.

## 13.4 Planned safety and other analyses

### 13.4.1 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized by MedDRA System Organ Class (SOC) and Preferred Term. The incidence of SAEs, AEs leading to premature discontinuation, and related AEs, and the incidence of AEs by maximum intensity will also be summarized.

### 13.4.2 Pharmacokinetic analyses

Descriptive statistics of plasma concentrations of BRV will be summarized by subgroups and total. Figures of BRV plasma concentration vs time profile will be produced by subgroups and total. As needed, population PK and/or PK analyses will be planned and described in a separate data analysis plan.

## 13.5 Handling of protocol deviations

After all eCRFs have been retrieved and entered and queries addressed, and prior to locking the clinical database and unblinding the study, a blinded DEM will be held. The purpose of this

blinded DEM will be to assess the quality of the data for subsequent database lock, identify protocol deviations, finalize analysis populations, reach agreement on the pooling of stratification levels for statistical analysis, and verify that the statistical assumptions for the primary analysis are appropriate.

## 13.6 Handling of dropouts or missing data

Subjects who provide at least 1 complete daily seizure record for the Treatment Period will be included in the primary analysis. Seizure frequency standardized to a 28-day duration will be computed over non-missing DRC days during each study period; missing seizure DRC days will not be considered in the calculation of seizure frequency. Similarly, if a subject prematurely discontinues before the end of the Treatment Period, then the seizure information collected up until the time of discontinuation will be used to calculate seizure frequency over the Treatment Period. The preceding assumes that seizure frequency during the missing DRC days is equal to the daily seizure frequency computed over non-missing days. Sensitivity analyses will be considered to assess the impact of these assumptions.

## 13.7 Planned interim analysis and data monitoring

No formal interim analysis is planned. However, an informal analysis is planned post data collection during the double-blind period of the study to support regulatory submissions. Prior to the analysis, an official unblinding will be completed. At a minimum, one interim report is planned. Regular monitoring of safety data collected during clinical studies will be performed by medically qualified Sponsor personnel or equivalent designee(s).

## 13.8 Determination of sample size

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

## 13.9 Management of LEV cap

The number of prior LEV users will be limited to 30% of the total study population. The system cap will be managed in IWRS. Operational aspects of the LEV cap will be specified in the Monitoring Plan.

# 14 ETHICS AND REGULATORY REQUIREMENTS

## 14.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

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

Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. Additionally, if applicable (according to subject's age and local requirements), the subject will sign an IRB/IEC-approved Assent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the Investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

## 14.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

## 14.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or 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 Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

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

### 14.4 Subject privacy

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

The Investigator 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 subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

### 14.5 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, and the regulatory authorities (if required), prior to being implemented.

## 15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

# 16 REFERENCES

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.

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# 17 APPENDIX

## 17.1 Appendix 1 - International Classification of Epileptic Seizures

**International Classification of Epileptic Seizures (1981)**

**I. Partial seizures (focal, local)**

***A. Simple partial seizures (consciousness not impaired)***

1. With motor signs
   a) Focal motor without march
   b) Focal motor with march (Jacksonian)
   c) Versive
   d) Postural
   e) Phonatory (vocalization or arrest of speech)
2. With somatosensory or special sensory symptoms (simple hallucinations, eg, tingling, light flashes, buzzing)
   a) Somatosensory
   b) Visual
   c) Auditory
   d) Olfactory
   e) Gustatory
   f) Vertiginous
3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation)
4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures.
   a) Dysphasic
   b) Dysmnesic (eg, déjà-vu)
   c) Cognitive (eg, dreamy states, distortions of time sense)
   d) Affective (fear, anger, etc.)
   e) Illusions (eg, macropsia)
   f) Structured hallucinations (eg, music, scenes)

***B. Complex partial seizures (with impairment of consciousness: may sometimes begin with simple symptomatology)***

1. Simple partial onset followed by impairment of consciousness
   a) With simple partial features followed by impaired consciousness (A.1. - A.4.)

b) With automatisms

2. With impairment of consciousness at onset

a) With impairment of consciousness only

b) With automatisms

***C. Partial seizures evolving to secondarily generalized seizures (this may be generalized tonic-clonic, tonic, or clonic)***

1. Simple partial seizures (A) evolving to generalized seizures
2. Complex partial seizures (B) evolving to generalized seizures
3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

**II. Generalized seizures (convulsive or non-convulsive)**

***A. 1. Absence seizures***

a) Impairment of consciousness only

b) With mild clonic components

c) With atonic components

d) With tonic components

e) With automatisms

f) With autonomic components

(b through f may be used alone or in combination)

***2. Atypical absence***

May have:

a) Changes in tone that are more pronounced than in A.1

b) Onset and/or cessation that is not abrupt

***B. Myoclonic seizures* - Myoclonic jerks (single or multiple)**

***C. Clonic seizures***

***D. Tonic seizures***

***E. Tonic-clonic seizures***

***F. Atonic seizures - (Astatic)***

(combinations of the above may occur, eg, B and F, B and D)

**III. Unclassified epileptic seizures**

Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, eg, rhythmic eye movements, chewing, and swimming movements.

**Status epilepticus** (prolonged partial or generalized seizures without recovery between attacks)

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22:489-501.

## 17.2 Appendix 2 - International Classification of Epilepsies and Epileptic Syndromes

**International Classification of Epilepsies and Epileptic Syndromes (1989)**

**1. Localization-related (focal, local, partial) epilepsies and syndromes**

**1.1 Idiopathic (with age-related onset)**

- Benign childhood epilepsy with centrotemporal spike
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

**1.2 Symptomatic**

- Chronic progressive epilepsia partialis continua of childhood (Rasmussen syndrome)
- Syndromes characterized by seizures with specific modes of precipitation
- Temporal lobe epilepsy
- Frontal lobe epilepsy
- Parietal lobe epilepsy
- Occipital lobe epilepsy

**1.3 Cryptogenic**

**2. Generalized epilepsies and syndromes**

**2.1 Idiopathic (with age-related onset − listed in order of age)**

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

**2.2 Cryptogenic or symptomatic (in order of age)**

- West syndrome (infantile spasms, Blitz-Nick-Salaam Krämpfe)
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures

- Epilepsy with myoclonic absences

**2.3 Symptomatic**

**2.3.1 Non-specific etiology**

- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression-burst
- Other symptomatic generalized epilepsies not defined above

**2.3.2 Specific syndromes**

**3. Epilepsies and syndromes undetermined whether focal or generalized**

**3.1 With both generalized and focal seizures**

- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Epilepsy with continuous spikes-waves during slow wave sleep
- Acquired epileptic aphasia (Landau-Kleffner-syndrome)
- Other undetermined epilepsies not defined above

**3.2 Without unequivocal generalized or focal features**

**4. Special syndromes**

**4.1 Situation-related seizures (Gelegenheitsanfälle, Occasional seizures)**

- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.

## 17.3 Appendix 3 - List of Antiepileptic Drugs

The following is a list of antiepileptic drugs (generic name):

- Acetazolamide
- Acetylpheneturide
- Amino (diphenylhydantoin) valeric acid
- Barbexaclone
- Beclamide
- Brivaracetam
- Carbamazepine
- Carisbamate
- Clobazam
- Clonazepam
- Diclofenamide
- Eslicarbazepine
- Ethadione
- Ethosuximide
- Ethotoin
- Felbamate
- Fosphenytoin
- Gabapentin
- Ilepcimide
- Lacosamide
- Lamotrigine
- Levetiracetam
- Mesuximide
- Metharbital
- Methylphenobarbital
- Mephenytoin
- Nitrazepam
- Oxcarbazepine
- Paramethadione
- Perampanel
- Phenacemide
- Pheneturide
- Phenobarbital

- Phensuximide
- Phenytoin
- Pregabalin
- Primidone
- Progabide
- Retigabine
- Rufinamide
- Stiripentol
- Sultiame
- Tiagabine
- Topiramate
- Trimethadione
- Valproic acid
- Valpromide
- Vigabatrin
- Zonisamide

Note: An AED that contains more than one compound in this list is not counted as 1 AED. The number of compounds contained in 1 AED is counted as the number of AED administered.
It is prohibited that subjects take Levetiracetam, or Brivaracetam other than IMP, during the study.

## 17.4 Appendix 4 - Protocol Amendment 1

This protocol has been amended to incorporate the following:

- New study details of allowing temporary BRV to act as rescue for patients entering MAP.
- Amended details for including at least one planned interim report for the purpose of supporting regulatory submissions.

In addition, minor administrative edits including typographical changes for formatting and/or spelling errors have been made.

The following shows the changes made in Amendment 1 compared to the original protocol, dated 17 Oct 2016.

### Modifications and changes

### Global changes

There were no global changes to the protocol during this amendment.

### Specific changes

### Change #1

STUDY CONTACT INFORMATION

Sponsor/Local Legal Representative

### Has been changed to:

Sponsor/Local Legal Representative in Japan

### Change #2

LIST OF ABBREVIATIONS

The following was removed from the list of abbreviations:

| | |
|---|---|
| ECD | electronic data capture |

### Change #3

1 SUMMARY

Additional study information:

If BRV is commercially available upon subject completion of the Treatment and Transition Period, subjects will receive BRV directly without entering the LTFU study or MAP.

### Change #4

5.1 Study Description

Additional study information:

If BRV is commercially available upon subject completion of the Treatment and Transition Period, subjects will receive BRV directly without entering the LTFU study or MAP.

### Change #5

### 5.1.1 Study duration per subjects

Additional study information:

As a procedure of MAP, the import license of medication for MAP is necessary. The process to obtain the import license starts after patient enrollment and can on occasions take a long time. To avoid a scenario where a subject cannot enter MAP due to the delayed importation of medication, a temporary period for providing BRV will be prepared as the rescue. Once medication for MAP is ready, a subject can start MAP.

## Change #6

Table 5-1: Schedule of study assessments

| Assessments | Prospective Baseline Period (8 weeks) | | | Treatment Period (12 weeks) | | | | Early discontinuation | Transition Period (2 weeks)/ Down Titration Period (4 weeks) | Study Drug-Free Period (2 weeks)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | V4 | V5 | V6 | V7 | EDV | V8 | Safety Visit |
| | W -8 | W -4 | W 0 | W 2 | W 4 | W 8 | W 12 | | W 14/W 16 | W 18 |
| Written informed consent | X | | | | | | | | | |
| Subject ID Card dispense | X | | | | | | | | | |
| Eligibility assessment | X[b] | X[b] | X[b] | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical/procedures history | X | | | | | | | | | |
| Epilepsy history | X | | | | | | | | | |
| Lifetime AED history | X | | | | | | | | | |
| Birth control | X | | | | | | | | | |
| Vital signs[c] | X | X | X | X | X | X | X | X[d] | X | X |
| Body weight and height[e] | X | | X | X | X | X | X | X | X | X |
| Physical examination | X | | X | | | | X | X[d] | X | X |
| Neurological examination | X | | X | | | | X | X[d] | X | X |
| Psychiatric and mental status | X | | X | | | | X | X[d] | X | X |
| ECG | X[f] | | | X | X | | X | X[d] | X[k] | X |
| EEG | X[g] | | | | | | | | | |
| CT scan/MRI | X[h] | | | | | | | | | |
| IVRS/IWRS | X | | X | X | X | X | X | X | | |
| Subject DRC dispensed | X | X | X | X | X | X | X | X | X[o] | |

## Has been changed to:

| Assessments | Prospective Baseline Period (8 weeks) | | | Treatment Period (12 weeks) | | | | Early discontinuation | Transition Period (2 weeks)/ Down Titration Period (4 weeks) | Study Drug-Free Period (2 weeks)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | V4 | V5 | V6 | V7 | EDV | V8 | Safety Visit |
| | W -8 | W -4 | W 0 | W 2 | W 4 | W 8 | W 12 | | W 14/W 16 | W 18 |
| Written informed consent | X | | | | | | | | | |
| Subject ID Card dispense | X | | | | | | | | | |
| Eligibility assessment | X[b] | X[b] | X[b] | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical/procedures history | X | | | | | | | | | |
| Epilepsy history | X | | | | | | | | | |
| Lifetime AED history | X | | | | | | | | | |
| Birth control | X | | | | | | | | | |
| Vital signs[c] | X | X | X | X | X | X | X | X | X | X |
| Body weight and height[e] | X | | X | X | X | X | X | X | X | X |
| Physical examination | X | | X | | | | X | X[d] | X | X |
| Neurological examination | X | | X | | | | X | X[d] | X | X |
| Psychiatric and mental status | X | | X | | | | X | X[d] | X | X |
| ECG | X[f] | | | X | X | | X | X[d] | X[k] | X |
| EEG | X[g] | | | | | | | | | |
| CT scan/MRI | X[h] | | | | | | | | | |
| IVRS/IWRS | X | | X | X | X | X | X | X | X | |
| Subject DRC dispensed | X | X | X | X | X | X | X | X[d] | X[o] | |

## Change #7

7.8.1 Permitted concomitant treatments (medication and therapies)

All subjects will take a minimum of 1 or 2 concomitant AEDs (Appendix 3 [Section 17.3]). Only daily use is permitted.

## Has been changed to:

All subjects will take 1 or 2 concomitant AEDs (Appendix 3 [Section 17.3]). Only oral-daily use is permitted (any other use or route of administration is prohibited, except when it is used as rescue medication).

## Change #8

7.8.3 Restricted concomitant treatments (medications and therapies)

Additional restriction:

Any drug where the route of administration is not oral, except when it used as rescue medication.

## Change #9

7.8.3 Rescue medication

Additional criteria:

In addition, the use of anticonvulsants are permitted as rescue medication.

## Change #10

8.8 Early Discontinuation Visit (after randomization)

Bullet 7:

- IVRT/IWRT

## Has been changed to:

- IVRS/IWRS

## Change #11

8.9 Visit 8 (Transition Period)

Additional assessment added to Visit 8:

- IVRS/IWRS

## Change #12

8.9.1 Visit 8 (Down-Titration Period)

Additional assessment added to Visit 8:

- IVRS/IWRS

## Change #13

11.2 Laboratory measurements

Table 11-1: Laboratory measurements

| Hematology | Biochemistry | Urinalysis | Pregnancy |
|---|---|---|---|
| WBC | Glucose | Glucose | β-hCG urine/ serum |
| RBC | Sodium | Ketones | |
| Hemoglobin | Potassium | Occult blood | |
| Hematocrit | Calcium | Protein | |
| MCV | Chloride | Nitrites | |
| MCH | Bicarbonate | Leukocytes | |
| MCHC | Phosphorus (inorganic) | Microscopic examination[b] | |
| Platelet count | Total protein | | |
| Lymphocytes (number, %) | Albumin | | |
| Monocytes (number, %) | Total bilirubin[a] | | |
| Neutrophils (number, %) | ALP[a] | | |
| Eosinophils (number, %) | AST (SGOT)[a] | | |
| Basophils (number, %) | ALT (SGPT)[a] | | |
| | GGT[a] | | |
| | Uric acid | | |
| | Urea | | |
| | Creatinine | | |
| | Triglycerides | | |
| | Cholesterol | | |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; FSH=follicle stimulating hormone; GGT=gamma-glutamyltransferase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SerV=Screening Visit; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=tetraiodothyronine; TSH=thyroid stimulating hormone; TV=titration visit; WBC=white blood cell

[a] This assessment is used for hepatic monitoring.
[b] Includes bacteria, cells, casts, and crystals for all samples.

## Has been changed to:

| Hematology | Biochemistry | Urinalysis | Pregnancy |
|---|---|---|---|
| WBC | Glucose | Glucose | β-hCG urine/ serum |
| RBC | Sodium | Ketones | |
| Hemoglobin | Potassium | Occult blood | |
| Hematocrit | Calcium | Protein | |
| MCV | Chloride | Nitrites | |
| MCH | Bicarbonate | Leukocytes | |
| MCHC | Phosphorus (inorganic) | Microscopic examination[b] | |
| Platelet count | Total protein | | |
| Lymphocytes (number, %) | Albumin | | |
| Monocytes (number, %) | Total bilirubin[a] | | |
| Neutrophils (number, %) | ALP[a] | | |
| Eosinophils (number, %) | AST (SGOT)[a] | | |
| Basophils (number, %) | ALT (SGPT)[a] | | |
| | GGT[a] | | |
| | Uric acid | | |
| | Urea | | |
| | Creatinine | | |
| | Triglycerides | | |
| | Cholesterol | | |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; GGT=gamma-glutamyltransferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; WBC=white blood cell

[a] This assessment is used for hepatic monitoring.
[b] Includes bacteria, cells, casts, and crystals for all samples.

## Change #14

11.2.1 Evaluation of PDILI

Table 11-2: Required Investigators and follow-up for PDILI, fourth row:

| **Laboratory value** | | | **Immediate** | | **Follow up** | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |
| ≥3xULN (and ≥2x Baseline) and <5xULN | <2xULN | No | Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met. | • Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2).<br>IMP discontinuation required if any of the following occur:<br>• Subject cannot comply with monitoring schedule.<br>• Liver chemistry values continue to increase.<br>Liver chemistry values remain ≥3xULN (and ≥2xBaseline) after 2 week monitoring without stabilization or evidence of resolution. | Not required unless otherwise medically indicated (at discretion of Investigator | Monitoring of liver chemistry values at least twice per week for 2 weeks[d]<br>Immediate IMP discontinuation required if:<br>• liver chemistry values continue to increase.<br>After 2 weeks of monitoring liver chemistry values:<br>• Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without stabilization or evidence of resolution<br>Continue to monitor until values normalize, stabilize, or return to within Baseline values[d] |

## Has been changed to:

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |
| ≥3xULN (and ≥2x Baseline) and <5xULN | <2xULN | No | Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met. | • Further investigation – immediate IMP discontinuation not required (see Section 11.2.1.2).<br>IMP discontinuation required if any of the following occur:<br>• Subject cannot comply with monitoring schedule.<br>• Liver chemistry values continue to increase.<br>Liver chemistry values remain ≥3xULN (and ≥2xBaseline) after 2 week monitoring without stabilization or evidence of resolution. | Not required unless otherwise medically indicated (at discretion of Investigator | Monitoring of liver chemistry values at least twice per week for 2 weeks[d]<br>Immediate IMP discontinuation required if:<br>• liver chemistry values continue to increase.<br>After 2 weeks of monitoring liver chemistry values:<br>• Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without stabilization or evidence of resolution<br>Continue to monitor until values normalize, stabilize, or return to within Baseline values[d] |

## Change #15

11.3.6 Body weight and height

At all visits, body weight (subject wearing light clothing without shoes) will be measured. Subjects with a body weight ≥40kg during Baseline Period will not be eligible. Height will be recorded at Baseline (Visit 1) only.

## Has been changed to:

At all visits, body weight (subject wearing light clothing without shoes) will be measured. Subjects with a body weight ≥40kg during Baseline Period will be eligible. Height will be recorded at Baseline (Visit 1) only.

## Change #16

11.3.8 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for Baseline/Selection as well as to assess suicidal ideation and behavior that may occur during the study. The C SSRS will be completed at time points specified in the schedule of study assessments (Table 5–1).

## Has been changed to:

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for Baseline/Selection as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed at time points specified in the schedule of study assessments (Table 5–1).

## Change #17

13.7 Planned interim analysis and data monitoring

No interim analyses are planned for this study.

## Has been changed to:

No formal interim analysis is planned. However, an informal analysis is planned post data collection during the double-blind period of the study to support regulatory submissions. Prior to the analysis, an official unblinding will be completed. At a minimum, one interim report is planned. Regular monitoring of safety data collected during clinical studies will be performed by medically qualified Sponsor personnel or equivalent designee(s).

## Change #18

17.1 Appendix 1

## Has been changed to:

17.1 Appendix 1 - International Classification of Epileptic Seizures

## Change #19

17.2 Appendix 2

## Has been changed to:

17.2 Appendix 2 - International Classification of Epilepsies and Epileptic Syndromes

## Change #20

17.3 Appendix 3

## Has been changed to:

17.3 Appendix - List of Antiepileptic Drugs

## Change #21

Additional appendix:

17.4 Appendix 4 –Protocol Amendment 1

## 17.5 Appendix 5 – Protocol Amendment 2

This protocol has been amended to incorporate the following:

- A change described in Appendix 4 of Protocol Amendment 1 (dated 12 May 2017) was not incorporated in the relevant section of the protocol amendment. This change has been made to reflect that amendment.

In addition, minor formatting corrections have been made to a sub-section.

The following shows the changes made in Protocol Amendment 2 compared to Protocol Amendment 1, dated 12 May 2017.

### Modifications and changes

### Global changes

There were no global changes to the protocol during this amendment.

### Specific changes

### Change #1

Additional term to the abbreviation list:

EDV Early Discontinuation

### Change #2

7.8.2 Prohibited concomitant treatments (medication and therapies)

- - LEV
- - BRV (other than IMP)
- - Potassium bromide, sodium bromide, and calcium bromide
- - Other investigational products and drugs and medical devices that have not been approved in each country
- -Brain surgery (including surgery for examination purposes).

### Has been changed to:

The following concomitant medications/treatments are prohibited during the study:

- LEV
- BRV (other than IMP)
- Potassium bromide, sodium bromide, and calcium bromide
- Other investigational products and drugs and medical devices that have not been approved in each country
- Brain surgery (including surgery for examination purposes).

### Change #3

7.8.3 Restricted concomitant treatments (medication and therapies)

The following concomitant medications/treatments are restricted during the study:

Drugs with possible CNS effects (anxiolytics, hypnotic, and neuropsychiatric agents) including benzodiazepines are allowed if at stable dose from at least 4 weeks prior to Visit 1 and during the entire study period. In case of as-needed use, it is allowed the frequency is up to once a week in this study. However, it is prohibited to take more than once a week in this study. Any drug where the route of administration is oral, except when it used as rescue.

## Has been changed to:

The following concomitant medications/treatments are restricted during the study:

Drugs with possible CNS effects (anxiolytics, hypnotic, and neuropsychiatric agents) including benzodiazepines are allowed if at stable dose from at least 4 weeks prior to Visit 1 and during the entire study period. In case of as-needed use, it is allowed the frequency is up to once a week in this study. However, it is prohibited to take more than once a week in this study. Any drug where the route of administration is not oral, except when it used as rescue medication.

## 17.6 Appendix 6 – Protocol Amendment 3

This protocol has been amended to incorporate the following:

- To include Non-Asian patients
- To include EU countries
- To raise the prior LEV limitation from 20% to 30%
- To ensure consistency between the protocol and CRF Completion Guidelines.

In addition, minor formatting and corrections have been made.

### Modifications and changes

### Global changes

The deletion of exclusive Asian population to include Non-Asian subjects.

Prior LEV limitation has been increased from 20% to 30%.

### Specific changes

| Section | Description of change | Rationale |
|---|---|---|
| Section 4.3 Safety variables | Added Section 4.3.1 Primary variable and Section 4.3.2 Exploratory variables | To define safety variables |
| Section 8.7 Early Discontinuation Visit (before randomization) | Updated section | For alignment with CRF Completion Guidelines |
| Throughout | Removed references to Asian subjects<br>Prior LEV limitations have been increased from 20% to 30% | Based on global |

## 17.7 Appendix 7 – Protocol Amendment 4

This protocol has been amended to incorporate the following:

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

In addition, minor administrative edits including typographical changes for formatting and/or spelling errors have been made.

### Modifications and changes

### Global changes

The "exploratory safety variable" language was changed to "other safety variable" throughout the protocol. The pharmacodynamic variables were also removed.

### Specific changes

### Change #1

**STUDY CONTACT INFORMATION, Sponsor/Local Legal Representative in Japan**

UCB Japan Co. Ltd.

Shinjuku Grand Tower

8-17-1 Nishi-Shinjuku

Shinjuku-ku

Tokyo 160-0023

JAPAN

**Has been changed to:**
**STUDY CONTACT INFORMATION, Sponsor/Local Legal Representatives**

| | | |
|---|---|---|
| UCB BIOPHARMA SRL | UCB Japan Co. Ltd. | **UCB Trading (Shanghai) Co., Ltd.** |
| **Allée de la Recherche 60** | Shinjuku Grand Tower<br>8-17-1 Nishi-Shinjuku<br>Shinjuku-ku | **317 Room No.439,<br>Futexi Yi road, China (Shanghai)<br>Pilot Free Trade Zone** |
| **1070 Brussels** | Tokyo 160-0023 | **Shanghai 200131** |

| | | |
|---|---|---|
| **BELGIUM** | JAPAN | **PRC** |

## Change #2

**STUDY CONTACT INFORMATION, Sponsor Study Physician**

| | |
|---|---|
| Address: | [redacted] Raffles City, Shanghai Office Tower,<br>268 Tibet Road Central, Shanghai 200001 PRC |

**Has been changed to:**

| | |
|---|---|
| Address: | [redacted] Raffles City, Shanghai Office Tower,<br>268 Tibet Road Central, Shanghai 200001 PRC |

## Change #3

**STUDY CONTACT INFORMATION, Clinical Project Manager**

| | |
|---|---|
| Name: | [redacted] |
| Address: | UCB Japan Co. Ltd.<br>Shinjuku Grand Tower, 8-17-1 Nishi-Shinjuku, Shinjuku-Ku,<br>Tokyo, 160-0023, JAPAN |
| Phone: | [redacted] |
| Fax: | [redacted] |

**Has been changed to:**

| | |
|---|---|
| Name: | [redacted] |
| Address: | **Allée de la Recherche 60**<br>**B- 1070 Brussels, BELGIUM** |
| Phone: | [redacted] |
| Fax: | [redacted] |

## Change #4

**SERIOUS ADVERSE EVENT REPORTING**

**The following SAE reporting was added:**

| **Serious adverse event reporting (24 hours) for China only** | |
|---|---|
| **Fax** | **UCB China: +86-21-23210206** |
| **Email** | **UCB China: ds.China@ucb.com** |

## Change #5

**Section 1, Summary, last 2 paragraphs**

Pharmacokinetic variables include BRV (parent compound only) plasma levels.

Safety variables include adverse events (AEs), laboratory tests (blood chemistry, hematology, urinalysis), electrocardiogram (ECG), vital signs, body weight, physical and neurological examinations, and mental and psychiatric status.

The planned number of evaluable subjects will be a total of 504 (168 subjects per treatment group) for the primary efficacy analysis. The number of prior LEV use subjects will be limited to 30% of the total study population. It is planned to have those subjects recruited in approximately 100 centers.

**Has been changed to:**

Pharmacokinetic variable **is** BRV (parent compound only) plasma levels.

Safety variables include **incidence of treatment-emergent adverse events (TEAEs), incidence of TEAEs leading to study withdrawal, incidence of treatment-emergent serious adverse events (SAEs), changes in clinical** laboratory test **parameters** (blood chemistry, hematology, urinalysis), electrocardiogram (ECG) **parameters and findings, changes in** vital signs **(SBP, DBP, and pulse rate), changes in** body weight, physical and neurological examinations, and mental and psychiatric status.

The planned number of evaluable subjects will be a total of **444** (**148** subjects per treatment group) for the primary efficacy analysis. The number of prior LEV use subjects will be limited to 30% of the total study population. It is planned to have those subjects recruited in approximately **95** centers.

## Change #6

**Section 2.4, Safety with BRV, first and third paragraphs**

In the BRV clinical development program, 3822 subjects were exposed to BRV (unique exposures) as of 14 Jul 2016.

In addition, the safety of BRV as long-term adjunctive treatment is being evaluated in 2 ongoing LTFU studies (N01125 and N01379) and 3 completed LTFU studies (N01199, N01315, and N01372). The safety profile in the open-label extension studies (up to 8 years) was consistent to that observed in the short-term, PBO-controlled studies.

**Has been changed to:**

In the BRV clinical development program, **3970** subjects **have been** exposed to BRV (unique exposures) as of **14 Jan 2019**.

In addition, the safety of BRV as long-term adjunctive treatment **has been** evaluated in **5** LTFU studies (**N01125**, **N01379, N01199**, N01315, and N01372). The safety profile in the open-label extension studies (up to 8 years) was consistent to that observed in the short-term, PBO-controlled studies.

## Change #7

**Section 2.5, Study rationale, first paragraph**

This adequate and well-controlled study will be performed to provide data confirming the efficacy and safety of BRV as an AED and to support a marketing authorization application /

new drug application in Japan for BRV in the indication of adjunctive treatment in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization.

**Has been changed to:**

This adequate and well-controlled study will be performed to provide data confirming the efficacy and safety of BRV as an AED and to support a new drug application in Japan **and China** for BRV in the indication of adjunctive treatment in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization.

## Change # 8

**Section 4.1.1, Primary efficacy variable**

**The following sentence was removed**

The primary efficacy outcome is the percent reduction in partial seizure frequency over PBO based on ANCOVA.

## Change # 8

**Section 4.3.1, Primary safety variable**

The primary safety variable is AEs.

**Has been changed to:**

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

## Change # 9

**Section 4.3.2 Exploratory safety variables**

The exploratory safety variables are as follows:

- Laboratory tests (blood chemistry, hematology, urinalysis)
- ECG
- Vital signs
- Body weight
- Physical examination
- Neurological examination
- Mental status
- Psychiatric status

**Has been changed to:**

**Section 4.3.2 Other safety variables**

The **other** safety variables are as follows:

- Changes in **clinical** laboratory **test parameters** (blood chemistry, hematology, urinalysis)
- ECG **parameters and findings**
- **Changes** in vital signs **(SBP, DBP, and pulse rate)**
- **Changes in** body weight
- Physical examination
- Neurological examination
- Mental status
- Psychiatric status

## Change #10

**Section 5.1.1, Study duration per subject, second paragraph, second bullet**

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

**Has been changed to:**

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

## Change #11

**Section 5.1.2, Planned number of subjects and sites**

The planned number of evaluable subjects will be a total of 504 (168 subjects per treatment group) for the primary efficacy analysis. Of the 504 subjects, approximately 129 Japanese subjects and approximately 375 subjects from other countries will be randomized. The number of prior LEV use subjects will be limited to 30% of the total study population. Considering an anticipated screen failure rate of approximately 20%, approximately 630 subjects (162 Japanese subjects and 468 subjects from other countries) will be screened. It is planned to have those subjects recruited in approximately 100 sites.

**Has been changed to:**

The planned number of evaluable subjects for the primary efficacy analysis will be a total of **444** (**148** subjects per treatment group). The number of prior LEV use subjects will be limited to 30% of the total study **population as referenced in Section 13.9**.

Considering an anticipated screen failure rate of approximately 20%, approximately **555** subjects will be screened. It is planned to have those subjects recruited in approximately **95 sites (50 Japan sites, 20 Southeast Asia sites in countries and regions specified in Section 5.1.3, and 25 China Mainland sites).**

## Change #12

**Section 5.1.3, Anticipated regions and countries**

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

**Has been changed to:**

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

## Change #13

**Section 6.2, Exclusion criteria, criterion #20**

20. Subject has any clinical conditions (eg, bone marrow depression, severe renal impairment) which impair reliable participation in the study or necessitate the use of medication not allowed by protocol.

**Has been changed to:**

20**a**. Subject has any clinical conditions (eg, bone marrow **suppression**, severe renal impairment **with creatinine clearance [CLcr] <30 ml/min/1.73 $m^2$)** which impair reliable participation in the study or necessitate the use of medication not allowed by protocol.

## Change #14

**Section 6.2, Exclusion criteria, criterion #27**

27. Subject has clinically significant deviations from reference range values for laboratory parameters: creatinine clearance (CLcr) calculated <50mL/min, platelets <100,000/µL, neutrophil cells <1,800/µL.

**Has been changed to:**

27**a**. Subject has clinically significant **laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results, according to the judgment of the Investigator**.

## Change #15

**The section below was added and following section numbers were adjusted accordingly:**

**7.9, Prior LEV use**

**Levetiracetam use within 90 days prior to Visit 1 [(Week -8) Baseline] is prohibited. If a subject has been treated with LEV in the past, in order to participate in the study:**

- **oral LEV must be discontinued ≥91 days prior to Visit 1, or**
- **intravenous (iv) LEV must have been administered ≥91 days prior to Visit 1.**

**The management of LEV cap is specified in Section 13.9.**

## Change #16

**Section 13.3.1, Analysis of the primary efficacy variable, last paragraph**

Statistical testing will be based on the comparison of each BRV treatment groups (BRV 50mg/day and 200mg/day) to PBO with control of overall Type I error rate based on the Hochberg procedure. The Hochberg procedure does not require a pre-specified order of testing

for BRV dose groups vs PBO. In a setting with a comparison of 2 active groups to PBO, the Hochberg procedure is applied by first testing the BRV group with the larger p-values with testing at the 0.05 level. If statistical significance is achieved at this step then the study is positive and both BRV dose groups are declared statistically different from PBO. If the largest p-values is not significant at the 0.05 level, then the Hochberg procedure steps to the smaller p-values with testing at the 0.025 level. If statistical significance is achieved at this step then the study is positive and the BRV dose group associated with the smaller p-values is declared statistically different from PBO. If the smaller p-values is not significant at the 0.025 level, then neither BRV group is statistically different from PBO and the study is not positive.

**Has been changed to:**

Statistical testing will be based on the comparison of each BRV treatment **group** (BRV 50mg/day and 200mg/day) to PBO with control of overall Type I error rate based on the Hochberg procedure. The Hochberg procedure does not require a pre-specified order of testing for BRV dose groups vs PBO. In a setting with a comparison of 2 active groups to PBO, the Hochberg procedure is applied by first testing the BRV group with the larger **p-value** at the 0.05 level. If statistical significance is achieved at this step, then the study is positive and both BRV dose groups are declared statistically different from PBO. If the largest **p-value** is not significant at the 0.05 level, then the Hochberg procedure steps to the smaller **p-value** and tests at the 0.025 level. If statistical significance is achieved at this step, then the study is positive and the BRV dose group associated with the smaller **p-value** is declared statistically different from PBO. If the smaller **p-value** is not significant at the 0.025 level, then neither BRV group is statistically different from PBO and the study is not positive.

## Change #17

**Section 13.3.2, Analysis of secondary efficacy variable, fourth paragraph**

Median percent change in partial seizure frequency per 28 days from Baseline to the Treatment Period will be compared between each BRV group and PBO using a Wilcoxon-Mann-Whitney test. Hodges Lehmann non-parametric effect estimates and corresponding 95% confidence intervals will be provided. Categorized percent change in partial seizure frequency from Baseline to the Treatment Period will be summarized descriptively with comparisons between each BRV group and PBO carried out using a Mantel-Haenszel test for comparison of row mean scores. Seizure freedom rates will be compared between each BRV group and PBO using Fisher's Exact Test. To be considered seizure-free, a subject must not report seizures of any type and must complete the Treatment Period without any missing seizure DRC days.

**Has been changed to:**

Median percent **reduction** in partial seizure frequency per 28 days from Baseline to the Treatment Period will be compared between each BRV group and PBO using a Wilcoxon-Mann-Whitney test. Hodges Lehmann non-parametric effect estimates and corresponding 95% confidence intervals will be provided. Categorized percent **reduction (<-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%)** in partial seizure frequency from Baseline to the Treatment Period will be summarized descriptively with comparisons between each BRV group and PBO carried out using a Mantel-Haenszel test for comparison of row mean scores. Seizure freedom rates will be compared between each BRV group and PBO using

Fisher's Exact Test. To be considered seizure-free, a subject must not report seizures of any type and must complete the Treatment Period without any missing seizure DRC days.

## Change #18

**Section 13.8, Determination of sample size**

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

**Has been changed to:**

A total of **148** analyzable subjects per treatment group will provide **at least** 80% power to simultaneously detect differences between **each** BRV treatment group (BRV 50mg/day group and BRV 200mg/day group) and **the** PBO group at the 1-sided 0.025 significance level. **This sample size assumes** treatment differences of 0.**221** and 0.**285** in means on the log-transformed scale and a common SD of 0.66. The estimates of 0.**221** and 0.**285** correspond to reductions of 19.**8**% and **24.8**% of BRV over PBO after back-transformation, respectively. The percent reduction of **24.8**% is obtained from BRV 200mg/day in the N01358 study **and assuming the LEV cap of 30% is reached overall.** Based on a similar result from the Integrated Summary of Efficacy **and again assuming the LEV cap of 30% is reached overall**, a 19.8% reduction of BRV 50mg/day over PBO can be estimated. The SD of 0.66 is based on the observed SD from all treatment groups in N01358. **The sample size calculation accounts for the correlation of the test statistics (same placebo group is compared to each BRV dose) as well as the planned Hochberg procedure.** A total of **444 (148×3)** analyzable subjects in the study is calculated as a target number.

## Change #19

**The following section was added:**

**13.9 Management of LEV cap**

**The number of prior LEV users will be limited to 30% of the total study population. The system cap will be managed in IWRS. Operational aspects of the LEV cap will be specified in the Monitoring Plan.**

# 18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

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

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

The objectives and content of this 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.

Investigator:

| | |
|---|---|
| Printed name | Date/Signature |

# 19 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

# Approval Signatures

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