PROTOCOL EP0087

A MULTICENTER, OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, ACTIVE-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF BRIVARACETAM ADMINISTERED INTRAVENOUSLY AS TREATMENT FOR INCREASED SEIZURE ACTIVITY IN AN EPILEPSY MONITORING UNIT SETTING

PHASE 2

IND Number: 103908

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Final Protocol	28 Jul 2016	Not applicable
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SERIOUS ADVERSE EVENT REPORTING

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARS	acute repetitive seizure
AST	aspartate aminotransferase
BRV	brivaracetam
CDMS	clinical data management system
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report form
EMU	Epilepsy Monitoring Unit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
LEV	levetiracetam
LZP	lorazepam
PET	positron emission tomography
PK	pharmacokinetic
PR	pulse rate

PP	per protocol
PS	Patient Safety
RR	respiratory rate
SAE	serious adverse event
SAGE	Self-Administered Gerocognitive Examination
SBP	systolic blood pressure
SFU	Safety Follow-Up
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 SUMMARY

EP0087 is an open-label, randomized, parallel-group, active-controlled study to assess the efficacy and safety of brivaracetam (BRV) administered intravenously as treatment for increased seizure activity in an epilepsy monitoring unit (EMU) setting. The primary objective is to assess the efficacy of intravenous (iv) BRV compared to iv lorazepam (LZP) in subjects with epilepsy undergoing EMU evaluation who experience seizures that require prompt treatment.

Subjects will be 18 to 70 years of age, will have an established diagnosis of epilepsy, and will be admitted to an institution's EMU for seizure characterization or noninvasive presurgical evaluation. Upon admission to the EMU (after screening), the subject will be randomly assigned (1:1:1) to receive a single iv dose of BRV 100mg, BRV 200mg, or LZP.

The primary efficacy variable is time to next seizure per clinical observation with EEG confirmation or rescue medication. The secondary efficacy variables are proportion of subjects seizure-free per clinical observation at 6 hours, 8 hours, and 12 hours after the end of study drug administration, and proportion of subjects who receive rescue medication during the 6 hours, 8 hours, and 12 hours after the end of study drug administration.

The other efficacy variable is time until seizure is resolved without additional intervention per clinical observation for those actively seizing at the end of study drug administration.

The pharmacokinetic variable is plasma concentration of BRV.

Safety variables are adverse events (AEs), assessment of cognitive impairment, vital signs, oxygen saturation, electrocardiogram (ECG), and occurrence of status epilepticus.

Study drug administration will begin when the Investigator or designee determines by clinical observation and electroencephalogram (EEG) that a seizure requiring intervention (ie, qualifying seizure) has started. The subject's seizure activity, by clinical observation and EEG, will be assessed over the next 12 hours following the end of study drug administration. In addition, the subject's cognitive impairment, vital signs, oxygen saturation, and ECG will be measured at specified time points. If the subject's seizure activity does not stop after administration of study drug or seizure activity recurs, the subject may receive rescue medication at the Investigator's discretion. Approximately 60 subjects will be enrolled in order to have 45 subjects (15 subjects per group) qualifying for primary analysis at up to 20 sites.

2 INTRODUCTION

Acute repetitive seizures (ARS), defined as recurrent seizures within 24 hours with recovery between seizures, are commonly treated with either benzodiazepines, a longer-acting AED, or a combination of both (Lowe et al, 2000). Early effective treatment suppresses seizure activity in order to prevent the detrimental effects of acute seizure exacerbation which may evolve into prolonged seizures or status epilepticus, resulting in lasting morphological and functional brain damage (Bergen, 2006). Benzodiazepines are effective at stopping seizure activity quickly but may be rapidly redistributed or have a short duration of action which may lead to a nonsustained clinical effect. In addition, benzodiazepines may cause respiratory depression and sedation, potentially leading to further complications.

The administration of longer acting AEDs may prevent recurrent seizures, improve outcomes, and reduce health-care costs by reducing hospitalizations. Brivaracetam, approved in 2016 by the

Food and Drug Administration (FDA) for adjunctive treatment of partial-onset seizures in adults, has a half-life of 9 hours. Evidence of efficacy of BRV in generalized seizures was shown for a subset of subjects with generalized epilepsy in a well-controlled, flexible-dose study (N01254). Positron emission tomography (PET) data from rhesus monkeys indicate that BRV penetrates the brain within minutes after iv administration (Mercier et al, 2015). In addition, data from a study conducted in patients with photoparoxysmal epilepsy (N01069) indicate that BRV produced an early and lasting effect in that model, with seizure activity suppressed at the earliest observed time point (0.5 hours). Taken together, BRV's profile suggests that it may act as fast as a benzodiazepine, protect against or prolong time to next seizure, and be better tolerated than a benzodiazepine with regards to sedation, cognitive impairment, and respiratory depression.

Intravenous BRV will be administered to subjects who have periods of increased epileptic seizure activity while being evaluated in an EMU. This population is comprised of subjects being intensively evaluated for partial-onset, generalized-onset, or mixed seizure disorders. These subjects are usually taking AEDs chronically and during the course of EMU evaluation the dose of 1 or more concomitant AEDs may be reduced. A subset of the EMU subjects will develop increased frequency of seizures which require treatment, usually with a benzodiazepine. Such study participants will be randomized to treatment with 1 of 2 doses of BRV or LZP, a benzodiazepine frequently used as rescue medication in the EMU setting. This study is intended to provide proof of concept. The efficacy results from this study will be used to aid selection of the optimal dose to evaluate in a future study in patients with ARS in the home setting.

UCB is collaborating with Evogen, Inc, for further development of EvoScore™ START, Evogen's new proteomics-based blood test designed to accurately distinguish epileptic seizures from other events. Subjects in this study will be asked to provide blood samples for assay refinement.

3 STUDY OBJECTIVES

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

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

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

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

4.1.2 Secondary efficacy variables

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

- Proportion of subjects who receive rescue medication during the 6 hours, 8 hours, and 12 hours after the end of study drug administration

4.1.3 Other efficacy variables

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

4.2 Safety variables

4.2.1 Adverse events

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

4.3 Pharmacokinetic variable

- plasma concentration of BRV at 1 hour and 5 hours after the end of BRV study drug administration

5 STUDY DESIGN

5.1 Study description

Subjects admitted to an institution's EMU for seizure characterization or noninvasive presurgical evaluation will be enrolled in this study. Upon admission to the EMU and after screening, the subject will be randomly assigned (1:1:1) to receive a single iv dose of BRV 100mg, BRV 200mg, or LZP. The number of subjects using levetiracitam (LEV) as concomitant AED will be limited to 25% of the total number of subjects who receive study drug.

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

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

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

oxygen saturation, and ECG will be measured at specified time points. Blood samples will be obtained at specified time points.

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

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

5.1.1 Study duration per subject

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

Screening Period: up to 28 days for consenting, planning EMU stay, randomization, and inpatient EMU time prior to the seizure qualifying for study drug administration.

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

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

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

5.1.2 Planned number of subjects and sites

Approximately 60 subjects will be enrolled in order to have 45 subjects (15 subjects per group) qualifying for primary analysis at up to 20 sites. Additional subjects may also be enrolled at the discretion of the Sponsor if subjects are replaced.

5.1.3 Anticipated regions and countries

This study will be conducted in the US.

5.2 Schedule of study assessments

Table 5–1: Schedule of study assessments

Assessments	Screening Period (Day -28 to Day -1; includes consenting, planning EMU stay, randomization, inpatient EMU time prior to the seizure qualifying for study drug administration)		Treatment Period (Day 1; start of study drug administration to 12h after end of study drug administration or until seizure or rescue medication)	Safety Follow-Up (24h after end of study drug administration)[a]
	Visit 1		Visit 2	Visit 3
	Screening	Prior to randomization		
Informed consent	X			
Inclusion/exclusion criteria	X	X	X	
Medical history[b]	X	X		
Concomitant medications	X	X	X	X
Demographic data	X			
Brief physical examination, including weight and height	X		X[c]	X[d]
Brief neurological examination	X		X[c]	X[d]
Laboratory assessment		X[e]		X
Withdrawal criteria		X	X	
Cognitive impairment (SAGE)		X	X[f]	
Oxygen saturation		X	X[g]	X[g]
Vital signs (SBP, DBP, PR, RR)		X	X[g]	X[g]
ECG[k]		X	X[h]	X

Table 5–1: Schedule of study assessments

Assessments	Screening Period (Day -28 to Day -1; includes consenting, planning EMU stay, randomization, inpatient EMU time prior to the seizure qualifying for study drug administration)		Treatment Period (Day 1; start of study drug administration to 12h after end of study drug administration or until seizure or rescue medication)	Safety Follow-Up (24h after end of study drug administration)[a]
	Visit 1		Visit 2	Visit 3
	Screening	Prior to randomization		
Adverse events	X	X	X	X
Randomization to study drug group[i]		X		
Seizure activity record per clinical observation and EMU's EEG data capture		X	X	X
Study drug administration[j]			X	
Blood sample collection			X[l]	X[l]

Table 5–1: Schedule of study assessments

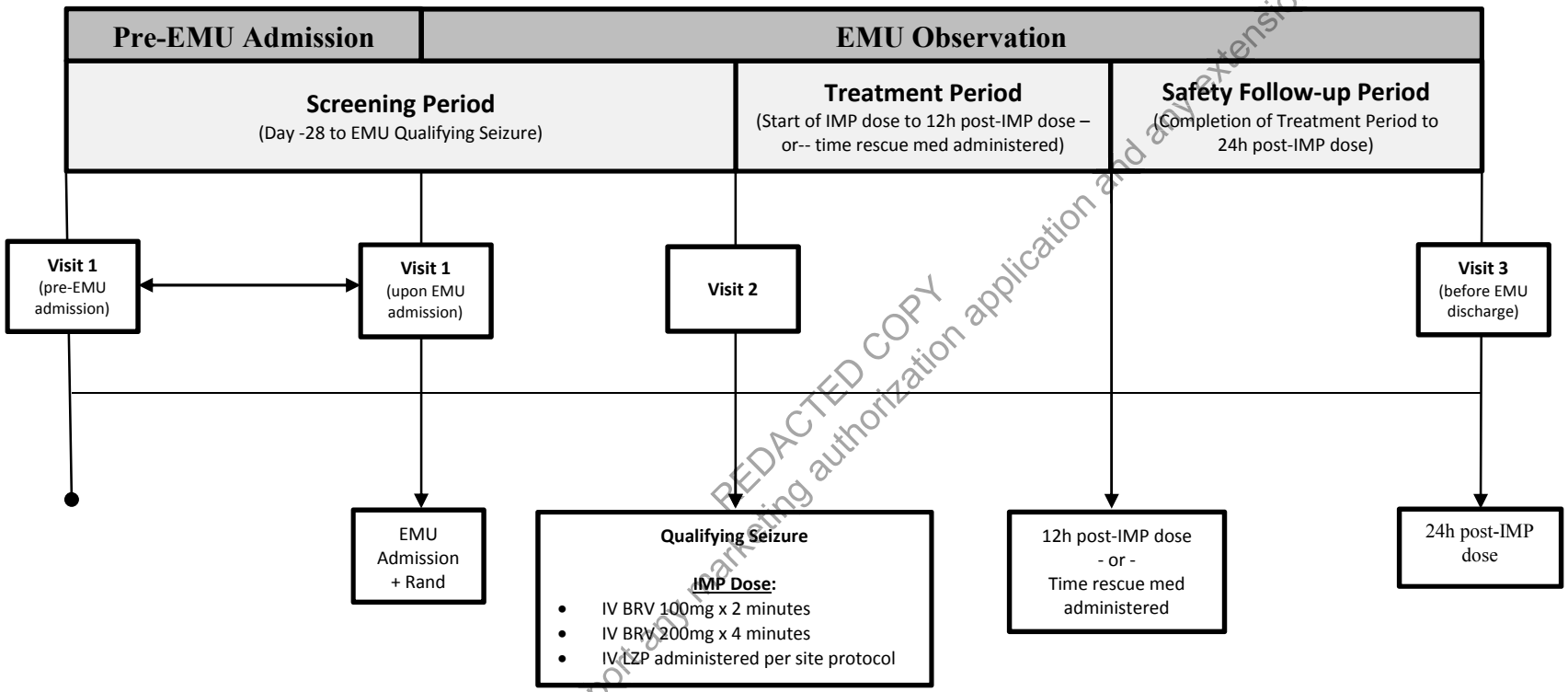
Assessments	Screening Period (Day -28 to Day -1; includes consenting, planning EMU stay, randomization, inpatient EMU time prior to the seizure qualifying for study drug administration)		Treatment Period (Day 1; start of study drug administration to 12h after end of study drug administration or until seizure or rescue medication)	Safety Follow-Up (24h after end of study drug administration)[a]
	Visit 1		Visit 2	Visit 3
	Screening	Prior to randomization		

BRV=brivaracetam; DBP=diastolic blood pressure; ECG=electrocardiogram; EEG=electroencephalogram; EMU=Epilepsy Monitoring Unit; iv=intravenous; PR=pulse rate; RR=respiratory rate; SAGE=Self-Administered Gerocognitive Examination; SBP=systolic blood pressure; SFU=Safety Follow-Up

[a] Safety Follow-Up assessments to be performed at least 24h after study drug administration.
[b] Medical history including psychiatric and substance abuse history.
[c] If the Screening physical and neurological examinations were performed within 7 days of Treatment Period, do not repeat.
[d] If any clinically significant abnormality observed after study drug administration, then perform at SFU.
[e] If subject has had laboratory assessments performed within the past 14 days, do not repeat.
[f] Assessment performed at Screening (Form 1), and at 1h (Form 2), 2h (Form 3), and 3h (Form 4) after the end of study drug administration. If study drug administration occurs for a nocturnal seizure and subject is asleep, assessment should not be performed.
[g] Assessments performed at the following time points: predose, end of bolus, 5min (±3min), 15min (±5min), 30min (±10min), 1h, 2h, and 4h (±15min) after end of bolus, unless seizure or rescue medication occurs that ends the Treatment Period. If clinically significant abnormality is observed in the final assessment of the Treatment Period, continue to monitor every 4h until resolution or end of SFU Period.
[h] Assessments will be performed within 60min after the start of study drug administration, and a 5min continuous ECG will be performed beginning with the bolus start and stopping 2 to 5min after the end of the bolus.
[i] Occurs after eligibility criteria have been confirmed.
[j] Subject must have a qualifying seizure (see Section 5.1).
[k] If abnormalities are noted, a 12-lead ECG may be administered for further assessment.
[l] Blood draws at 1h (±15min), 5h (±30min), 12h (±1h) and 24h (±3h) after end of study drug administration.

5.3 Schematic diagram

Figure 5–1: Schematic diagram



BRV=brivaracetam; EMU=Epilepsy Monitoring Unit; IMP=investigational medicinal product; LZP=lorazepam
Screening Period: up to 28 days for consenting, planning EMU stay, randomization after screening at the EMU admission, inpatient EMU time prior to the seizure qualifying for study drug administration.
Treatment Period: beginning at start of study drug administration when the subject has a qualifying seizure (see Section 5.1) and lasts up to 12 hours after the end of study drug administration or until a seizure occurs or rescue medication is given

5.4 Rationale for study design and selection of dose

Intravenous BRV will be administered to subjects who have periods of increased epileptic seizure activity while being evaluated in an EMU. This population is comprised of subjects being intensively evaluated for partial-onset, generalized-onset, or mixed seizure disorders. These subjects are usually taking AEDs chronically, and during the course of EMU evaluation, the dose of 1 or more concomitant AEDs may be reduced. A subset of the EMU subjects will develop increased frequency of seizures which require treatment, usually with a benzodiazepine. Such study participants will be randomized to treatment with BRV 100mg, BRV 200mg, or LZP, a benzodiazepine frequently used as rescue medication in the EMU setting.

As noted in the approved US product information, chronic administration of BRV (25mg to 100mg twice daily) provides no additional benefit when added to LEV in adult patients with partial onset seizures. However, it is unknown whether patients taking a stable dose of LEV or down-titrating LEV who experience seizures that require prompt treatment might benefit from acute administration of a higher dose of BRV (100mg or 200mg). Learning the outcome of these possible scenarios in the controlled environment of an EMU may be beneficial for clinicians.

The doses of BRV selected were based on the total daily doses in the US label and EU Summary of Product Characteristics, and modeling of plasma concentrations resulting from single iv doses up to 200mg. In addition, data on BRV in patients with generalized seizures were considered from the Phase 3 study N01254.

The safety and tolerability of iv administration of BRV 100mg bid has been evaluated in a Phase 3 study (N01258) in patients with epilepsy. Treatment with iv BRV (both bolus and infusion: 100mg bid) was well-tolerated.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

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.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is male or female, 18 to 70 years of age, inclusive.
4. Subject has an established diagnosis of epilepsy.
5. Subject has been admitted to the institution's EMU for seizure characterization or noninvasive presurgical evaluation or such admission is planned within 21 days of Screening.

6.2 Exclusion criteria

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

1. Subject has previously participated in this study and was treated with study drug. Re-screen is permitted.

2. Subject has participated in another study of an investigational medicinal product (IMP) or a medical device within the previous 30 days of EMU admission or is currently participating in another study of an IMP or a medical device.
3. Subject has taken BRV in the 21 days prior to EMU admission.
   a) Subject has taken LEV in the 21 days prior to EMU admission after the LEV enrollment cap is met (see Section 5.1)
4. History or presence of status epilepticus during the 6 months prior to EMU admission.
5. Subject has a 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 (eg, major surgery within the 2 weeks prior to screening).
6. Subject has >2x upper limit of normal (ULN) 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 Case Report form (CRF).

   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.

   Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.
7. Subject has chronic liver disease.
8. Subject has hypersensitivity to BRV or any of its excipients.
9. Subject has a history of alcohol or drug abuse during the 6 months prior to EMU admission.
10. Subject with a history of psychogenic seizures.
11. Subject is a pregnant or lactating female.
12. Subject has a history of a significant AE due to a benzodiazepine in the opinion of the Investigator.
13. Subject has respiratory failure (or is at risk for respiratory failure), untreated sleep apnea, or other severe cardiorespiratory disease with New York Heart Association Class III or IV functional status, or requires supplemental oxygen.
14. Subject has acute narrow-angle glaucoma or myasthenia gravis.
15. Subject is receiving benzodiazepine treatment (defined as an average of ≥4 administrations per week) that started less than 28 days prior to EMU admission.

16. Subject has a known allergic reaction or intolerance to benzodiazepines or benzodiazepine excipients.

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:

1. Subject develops an illness or complication that would interfere with his/her continued participation. This includes the initiation of a sedative medication that may interfere with the safety evaluations, such as sedative antipsychotics, opioids, or H1 antihistamines.
2. Investigator determines there is need to discontinue the study drug and administer a different treatment (eg, seizures are increasing in frequency or duration).
3. Any situation where, in the opinion of the Investigator, continued participation in the study would not be in the best interest of the subject.
4. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
5. Subject withdraws his/her consent.
6. The sponsor or a regulatory agency requests withdrawal of the subject.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. 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 electronic Case Report form (eCRF) must document the primary reason for withdrawal or discontinuation.

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

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

During the Screening Period, upon EMU admission and after screening assessments are completed, subjects will be randomly assigned (1:1:1) to receive a single iv dose of BRV 100mg, BRV 200mg, or LZP.

7.2 Treatment(s) to be administered

Brivaracetam bolus, the contents of two 5mL vials (=100mg [10mL] of BRV) will be administered iv over approximately a 2-minute period.

Brivaracetam bolus, the contents of four 5mL vials (=200mg [20mL] of BRV) will be administered iv over approxinately a 4-minute period.

Lorazepam bolus is to be injected based on information from the patient leaflet/package insert. The rate of injection should not exceed 2.0mg/min. The LZP dose will be determined according to the Investigator's clinical judgment.

7.3 Packaging

Brivaracetam will be contained in 5mL vials containing 50mg (5mL) of BRV.

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 (GMP) 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 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.

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.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

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 reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB (or designee). 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

All drug administrations will be done under supervision of the Investigator or his designee. Compliance will be monitored by drug accountability. Drug accountability must be recorded on the Drug Accountability form.

7.8 Concomitant medication(s)/treatment(s)

For any treatment other than the investigational product, including over-the-counter products, an accurate record must be kept in the clinic chart (source documentation) and in the eCRF. This record should include the name of the drug (preferably the brand name), the dose, the date(s) of administration, and the indication for use.

7.8.1 Permitted concomitant treatments (medications and therapies)

Concomitant medications per the EMU's standard of care are permitted during the study. If receiving Concomitant AEDs, treatment should be kept stable after IMP administration during the Treatment Period unless the patient needs rescue medication. Concomitant AEDs can be administered at the Investigator's discretion after the Treatment Period ends (12 hours after study drug administration).

7.8.2 Prohibited concomitant treatments (medications and therapies)

Central nervous system depressants, unless at a stable dose, should be avoided during the study; however, their use is allowed based on the Investigator's clinical judgment.

7.8.3 Rescue medication

Rescue medication will be administered as necessary per the EMU's standard of care. If a subject is to stay in the EMU for further seizure characterization following administration of rescue medication, that subject may remain in the study awaiting a qualifying seizure. This scenario requires consultation with the Medical Monitor.

7.9 Blinding

This is an open-label study.

7.10 Randomization and numbering of subjects

A 1:1:1 central randomization stratified for LEV use will be used in the trial to ensure overall balance across the different treatment groups (LZP, BRV 100 mg, BRV 200 mg). To enroll a subject (Visit 1), the Investigator or designee will contact the interactive response technology (IRT) 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 IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject, the Investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the Investigator or designee of the subject's randomization number. The IRT 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

8.1 Day -28 to Day -1/Screening

Prior to any study activities, subject or legal representative will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with

regulatory requirements. Subject or legal representative will be given adequate time to consider any information concerning the study, given to them by the Investigator or designee.

As part of the informed consent procedure, subject or legal representative will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

- Obtain signed and dated written Informed Consent by subject/legal representative
- Inclusion/exclusion criteria
- Medical history, including psychiatric and substance abuse history
- Concomitant medications
- Demographic data
- Brief physical examination, including weight and height
- Brief neurological examination
- Adverse events

The following assessments will be performed prior to randomization:

- Inclusion/exclusion criteria
- Medical history, including psychiatric and substance abuse history
- Concomitant medications
- Adverse events
- Cognitive impairment (Self-Administered Gerocognitive Examination [SAGE]) (Form 1)
- Laboratory assessment
- Withdrawal criteria
- Oxygen saturation
- Vital signs (SBP, DBP, HR, RR)
- ECG
- Seizure activity record per clinical observation and EMU's EEG data capture

Once the assessments above are performed, the subject may be randomized.

8.2 Day 1 (Treatment Period)

The Treatment Period begins when the subject has a qualifying seizure (see Section 5.1) and study drug is administered and lasts up to 12 hours after the end of study drug administration or until a seizure occurs or rescue medication is given. The following procedures will be performed:

- Confirm inclusion/exclusion criteria
- Concomitant medications

- Brief physical examination, including height and weight, if not performed within 7 days of Day 1
- Brief neurological examination if not performed within 7 days of Day 1
- Withdrawal criteria
- Cognitive impairment (SAGE) at 1 hour (Form 2), 2 hours (Form 3), and 3 hours (Form 4) after the end of study drug administration
- Oxygen saturation at predose, end of bolus, 5 (±3) minutes, 15 (±5) minutes, 30 (±10) minutes, 1 hour, 2 hours, and 4 hours (±15 minutes) after end of bolus, unless seizure or rescue medication occurs that ends the Treatment Period
- Vital signs (SBP, DBP, PR, RR) at predose, end of bolus, 5 (±3) minutes, 15 (±5) minutes, 30 (±10) minutes, 1 hour, 2 hours, and 4 hours (±15 minutes) after end of bolus, unless seizure or rescue medication occurs that ends the Treatment Period
- ECG within 60min after the start of study drug administration. A 5-minute continuous ECG monitoring will be performed beginning with the start of the iv bolus and stopping 2 to 5 minutes after the end of the iv bolus
- Adverse events
- Study drug administration
- Seizure activity record per clinical observation and EMU's EEG data capture
- Blood sample collection at 1 hour (±15 minutes, 5 hours (±30 minutes), and 12 (±1) hours after the end of study drug administration

8.3 Safety Follow-Up Period

The SFU Period is the 24 hours after study drug administration. The following procedures will be performed:

- Concomitant medications
- Brief physical examination to be performed if any clinically significant abnormality observed after study drug administration
- Brief neurological examination to be performed if any clinically significant abnormality observed after study drug administration
- Oxygen saturation if clinically significant abnormality observed in the last assessment of the Treatment Period and not resolved at end of Treatment Period
- Vital signs (SBP, DBP, PR, RR) if clinically significant abnormality observed in the last assessment of the Treatment Period and not resolved at end of Treatment Period
- ECG
- Adverse events
- Seizure activity record per clinical observation and EMU's EEG data capture

- Blood sample collection at 1 hour (±15 minutes), 5 hours (±30 minutes), 12 (±1) hours, and 24 (±3) hours after the end of study drug administration

9 ASSESSMENT OF EFFICACY

Efficacy will be assessed by time to next seizure per clinical observation and EEG or rescue medication.

10 ASSESSMENT OF PHARMACOKINETIC VARIABLES

Plasma samples for assessment of BRV concentrations will be collected at 1 hour and 5 hours after study drug administration for subjects who received BRV.

The central laboratory will provide the Investigator with sampling supplies (labels, needles, tubes, and vials) and an instruction manual explaining how to process and ship blood samples.

Bioavailability analysis will be conducted by UCB.

11 BIOMARKER ASSAY REFINEMENT

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

Subject refusal of biomarker sample blood draws will not be considered a protocol deviation. Plasma samples for the biomarker assay refinement will be sent to Evogen.26 May 2017

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

An adverse event (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.

12.1.1.2 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 12.1.1.3], 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.)

12.1.1.2.1 Anticipated serious adverse events

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.1.2.3.

Table 12–1: Anticipated serious adverse events for the epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administrative site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion[a]
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

[a] Convulsion if consistent with the seizure type known for the subject.

12.1.1.3 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. For this study, the AEs of special interest include:

- Autoimmune nephritis
- Nephritis
- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and 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). In the event of this occurring, permission to contact the subject's primary healthcare professional would be sought to ensure further investigation and follow up.

Adverse events of special interest should be reported to the SAE fax and email using the SAE form. However, if not considered an SAE, no seriousness criterion should be indicated.

12.1.2 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, diary cards) employed in the study.

12.1.2.1 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, diary card) and the corresponding medical terminology should be clarified in the source documentation.

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

12.1.2.2 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

12.1.2.3 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.

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.

12.1.3 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, except for cases of Hy's Law which have been identified prior to treatment initiation, where the follow up for the subject is transferred to the primary healthcare professional.

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.

12.1.4 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:

- Safety Follow-Up assessments should be conducted 24 hours 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/contract research organization (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.

12.1.5 Suspected transmission of an infectious agent via a medicinal product

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.

12.1.6 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).

12.1.7 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.

12.2 Laboratory measurements

The following laboratory parameters will be measured:

Table 12–2: Laboratory measurements

Hematology	Chemistry
Basophils	Calcium
Eosinophils	Chloride
Lymphocytes	Creatinine
Atypical lymphocytes	Magnesium
Monocytes	Potassium
Neutrophils	Sodium
Hematocrit	Glucose
Hemoglobin	BUN
MCH	AST
MCHC	ALP
MCV	ALT
Platelet count	GGT
RBC count	Total bilirubin
WBC count	LDH

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

All laboratory assessments are to be performed locally. Data from the local laboratory will not be recorded on the eCRF but will be available upon request to evaluate any SAE due to abnormal laboratory values. Laboratory assessments performed within the past 14 days should not be repeated. Pregnancy testing (minimally by urine dipstick) is conducted locally at the time of admission to the EMU or before randomization.

12.3 Other safety measurements

12.3.1 ECG

An ECG will be performed at Screening upon admission to the EMU and within 60min after the start of study drug administration. A 5-minute continuous ECG will be performed beginning with the start of the iv bolus and stopping 2 to 5 minutes after the end of the iv bolus. An ECG will also be performed at SFU. The Investigator will determine whether the results of the ECG are

normal or abnormal and assess the clinical significance of any abnormalities. If significant abnormalities are noted during ECG monitoring, a 12-lead ECG should be recorded in order to capture and document these abnormalities. If available, the original ECG tracing will be signed or initialed and dated by the Investigator and retained as part of the source data. Copies of all ECG tracings will be retrieved for all subjects presenting treatment-emergent clinically significant abnormalities during the study.

12.3.2 Vital signs

Vital signs (SBP, DBP, PR, and RR) after 5 minutes rest will be measured upon EMU admission, and on Day 1 at predose, end of bolus, 5 (±3) minutes, 15 (±5) minutes, 30 (±10) minutes, 1 hour, 2 hours, and 4 hours (±15 minutes) after the end of bolus, unless seizure or rescue medication occurs that ends the Treatment Period. If a clinically significant abnormality is observed in the final assessment of the Treatment Period, vital signs will continue to be monitored every 4 hours until resolution or the end of the SFU Period.

12.3.3 Body weight and height

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) and height will be measured upon preadmission to the EMU only.

12.3.4 Physical examination

A brief/targeted physical examination will be performed at preadmission. If the physical examination at Screening was not performed within 7 days of Day 1, the physical examination will be repeated on Day 1. If any clinically significant abnormality is observed after study drug administration, then the physical examination will be performed at SFU. Clinically significant new or worsened abnormalities will have to be reported as AEs.

12.3.5 Neurological examination

A brief/targeted neurological examination will be performed at preadmission. If the neurological examination at Screening was not performed within 7 days of Day 1, the neurological examination will be repeated on Day 1. If any clinically significant abnormality is observed after study drug administration, then the neurological examination will be performed at SFU. Clinically significant new or worsened abnormalities will have to be reported as AEs.

12.3.6 Oxygen saturation

Oxygen saturation will be measured upon EMU admission, and on Day 1 at predose, end of bolus, 5 (±3) minutes, 15 (±5) minutes, 30 (±10) minutes, 1 hour, 2 hours, and 4 hours (±15 minutes), unless seizure or rescue medication occurs that ends the Treatment Period. If a clinically significant abnormality is observed in the final assessment of the Treatment Period, oxygen saturation will continue to be monitored every 4 hours until resolution or the end of the SFU Period.

12.3.7 Self-Administered Gerocognitive Examination

The SAGE consists of a 22-point evaluation and is a handwritten self-test of memory developed to facilitate the screening of mild cognitive impairment and early dementia. The SAGE will be completed by the subject at Screening (Form 1) and at 1 hour (Form 2), 2 hours (Form 3), and 3 hours (Form 4) after the end of study drug administration. A subject is allowed 20 minutes to

complete the SAGE. If study drug administration occurs near the subject's normal sleep cycle and the subject is asleep, the SAGE does not need to be performed (let the subject sleep).

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 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.

After implementation of such measure, the Investigator must notify the Clinical Project Manager (CPM) of the sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring Standard Operating Procedures (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.

13.2.1 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 eCRFs 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.

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, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

13.2.2 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 13.2.1.

13.3 Data handling

13.3.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic 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.

13.3.2 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. This study will be performed using remote data capture. The data are entered into the eCRFs once and are subsequently verified.

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

13.3.3 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.

13.4 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.

13.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

13.6 Audit and inspection

The Investigator 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 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).

13.7 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.

14 STATISTICS

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

14.1 Definition of analysis sets

The Randomized Set (RS) will consist of all subjects who are randomized.

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

The Per-Protocol (PP) Set will consist of all subjects in the ITT Set who did not have any important protocol deviations determined to impact the interpretation of the primary efficacy analysis.

All efficacy and safety analyses will be carried out using the ITT Set. Selected supportive efficacy analyses will be carried out using the PP Set.

14.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. 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. In such cases, unless otherwise specified, the analysis will be run both with and without the values. Any outliers will be reviewed during data review.

14.3 Planned efficacy analyses

14.3.1 Analysis of the primary efficacy variable

Time to next seizure (per clinical observation with EEG confirmation) or rescue medication, representing treatment failure, from the end of study drug administration to 12 hours after the end of study drug administration will be compared between each BRV arm and LZP using survival analysis methods; if the sample size is sufficient, a subgroup analysis using strata may be performed.

14.3.2 Other efficacy analyses

Time to next seizure (per clinical observation) or rescue medication from the end of study drug administration to 12 hours after the end of study drug administration will be compared between each BRV arm and LZP using survival analysis methods.

Seizure freedom rates at 6 hours, 8 hours, and 12 hours after the end of study drug administration will be compared between each BRV arm and LZP using Fisher's Exact Test.

Proportion of subjects who receive rescue medication during 6 hours, 8 hours, and 12 hours after study drug administration will be compared between each BRV arm and LZP using Fisher's Exact Test.

Time until seizure is resolved without additional intervention per clinical observation (only for those actively seizing at end of study drug administration) will be compared between each BRV arm and LZP using survival analysis methods.

14.4 Planned safety and other analyses

14.4.1 Safety analyses

Treatment-emergent adverse events (TEAEs) are defined as AEs which have onset on or after the time of initiation of the iv administration of study drug. The incidence of TEAEs, TEAEs leading to permanent discontinuation of study drug, and treatment-emergent serious adverse events will be summarized over the entire study.

Quantitative safety parameters will be summarized descriptively by time point. Categorical safety summaries will provide the number and percentage of subjects within each summarized category.

Observed values and changes from baseline (pre-dose) in vital signs, ECGs, and oxygen saturation will be summarized using continuous descriptive statistics.

Assessment of cognitive impairment will be summarized.

Progression to status epilepticus will be summarized.

14.5 Planned interim analysis and data monitoring

No interim analyses are planned for this study.

14.6 Determination of sample size

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

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 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. 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.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study-specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

15.2 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.

15.3 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.

15.4 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).

15.5 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.

16 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.

17 REFERENCES

Bergen DC. Do seizures harm the brain? Epilepsy Curr. 2006;6:117-8.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Mercier J, Deo AK, Holden D, et al. Brivaracetam achieves SV2A occupancy in the brain faster than levetiracetam. Epilepsy Curr. 2015;15(Suppl S1):323. Abstract 2.332.

Lowe MN, Palmer KJ, Wilde MI. Management of acute repetitive seizures: defining the role of rectal diazepam gel. Dis Manage Health Outcomes. 2000;8(6):355-68.

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

18.2 Protocol Amendment 1

The purpose of Amendment 1 was to clarify assessments and procedures, such as ECG, vital signs, reporting of adverse events of special interest, and the SAGE. In addition, qualifying seizures were further defined, the study contact information was updated, and allowance was made for enrollment of some subjects taking LEV. Amendment 1 also includes blood sampling at up to 4 time points after study drug administration; 2 time points for BRV bioavailability analysis and epilepsy biomarker assay development, as well as 2 more optional blood samples for assay refinement.

The major specific changes are detailed in Table 18–1. Some minor text changes or deletions to improve readability are not summarized.

Table 18–1: Summary of changes in EP0087 Protocol Amendment 1

Protocol section(s) impacted	Summary of previous protocol text	Summary of revised protocol text	Rationale
Study contact information	Sponsor Study Physician: [redacted] Clinical Trial Biostatistician: [redacted]	Sponsor Study Physician: [redacted] Clinical Trial Biostatistician: [redacted]	Change in study personnel
Sections 1, 4.2, 5.1, 8.1, 8.2, 8.3, 10.3.1, 12.4.1, and Table 5-1	A 12-lead ECG was required for routine screening and safety assessments	The EMU standard ECG is sufficient for routine screening and safety assessments. A 12-lead ECG may be used for further evaluation of abnormal ECG results.	A 1- or 3-channel ECG is standard of care in the EMU setting, and either will provide adequate monitoring of safety with the injections. A 12-lead ECG will still be used if abnormalities are observed.
Table 5-1	None	Added blood sample collection	PK and assay refinement variables added to protocol.

Protocol section(s) impacted	Summary of previous protocol text	Summary of revised protocol text	Rationale
Section 5.1	Timing of study drug administration relative to the qualifying seizure; clarification of the qualifying seizure definition, timing of re-introduction of AEDs	The study drug administration will begin within 30 minutes of the qualifying seizure, which is defined as any one of the following: ≥3 seizures per 24 hours; ≥2 seizures in 6 hours; any generalized tonic-clonic seizure requiring intervention, as determined by the Investigator. If rescue medication is administered, AEDs can be re-introduced once the subject is in the SFU Period.	Clarification
Section 5.4	Gives rationale for study design and selection of dose	Addition of language justifying concomitant LEV in some subjects.	As noted in the approved US product information, chronic administration of BRV (25mg to 100mg twice daily) provides no additional benefit when added to LEV in adult patients with partial onset seizures. However, it is unknown whether patients taking a stable dose of LEV or down-titrating LEV who experience seizures that require prompt treatment might benefit from acute administration of a higher dose of BRV (100mg or 200mg). Learning the outcome of these possible scenarios in the controlled environment of an EMU may be beneficial for clinicians.

Protocol section(s) impacted	Summary of previous protocol text	Summary of revised protocol text	Rationale
Section 6.2	Exclusion Criterion 3: Subject has taken BRV or LEV in the 21 days prior to EMU admission	Exclusion Criterion 3: Subject has taken BRV ~~or LEV~~ in the 21 days prior to EMU admission	As noted in the approved US product information, chronic administration of BRV (25mg to 100mg twice daily) provides no additional benefit when added to LEV in adult patients with partial onset seizures. However, it is unknown whether patients taking a stable dose of LEV or down-titrating LEV who experience seizures that require prompt treatment might benefit from acute administration of a higher dose of BRV (100mg or 200mg). Learning the outcome of these possible scenarios in the controlled environment of an EMU may be beneficial for clinicians.
Section 7.8.1	Describes permitted concomitant treatments	Addition of language: Concomitant AEDs can be re-introduced after the Treatment Period ends (12 hours after study drug administration).	Clarification on when concomitant AEDs can be given once subjects end treatment with study drug
Section 7.8.3	Defines rescue medication usage	Addition of language: If a subject is to remain in the EMU for further seizure characterization following administration of rescue medication, that subject may remain in the study awaiting a qualifying seizure. This scenario requires consultation with the Medical Monitor.	Allows for a subject to remain in the study after rescue medication is given and before study drug has been administered.

Protocol section(s) impacted	Summary of previous protocol text	Summary of revised protocol text	Rationale
Section 8.2	Outlines procedures performed during the Treatment Period	Added blood sample collection	Describes when blood samples are collected
Section 8.3	Outlines procedures performed during the Safety Follow-up Period	Added blood sample collection	Describes when blood samples are collected
Section 10	None	Added pharmacokinetic variable description	Describes new variable
Section 11	None	Added biomarker assay refinement	Describes assay refinement
Section 12.1.1.3	Defines AEOIs for this study	Addition of instructions for reporting an AESI.	Instructions
Section 12.2	Gives details on collection of laboratory measurements	Addition of language: Pregnancy testing (minimally by urine dipstick) is conducted locally at the time of admission to the EMU or before randomization.	Clarification that pregnancy testing must be done in the EMU upon admission or before randomization
Section 12.3.2	Describes procedures for collecting vital signs	Addition of time window around when vital signs are collected	Allows a small amount of flexibility in timing of vital signs collection so as not to risk protocol violation
Section 12.3.7	Describes procedures for administering the SAGE	Clarification that the SAGE need not be administered during the subject's normal sleep cycle	Removes burden of sleep disruption from subject

19 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

20 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.

EP0087 Protocol Amendment 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	26-May-2017 20:58 GMT+0
[redacted]	Clinical Approval	26-May-2017 22:09 GMT+0