PROTOCOL EP0085 AMENDMENT 4.0

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

PHASE 3

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Confidential Material

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BRV	brivaracetam
CDMS	clinical data management system
CLcr	creatinine clearance
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEM	data evaluation meeting
DRC	daily record card
ECG	electrocardiogram
eCRF	electronic Case Report form
EDC	electronic data capture
EDV	Early Discontinuation Visit
EEG	electroencephalogram
EV	Entry Visit
FEV	Full Evaluation Visits
FV	Final Visit
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
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
MEV	Minimal Evaluation Visits
MedDRA	Medical Dictionary for Regulatory Activities
PBO	placebo
PDILI	potential drug-induced liver injury
PK	pharmacokinetic
PS	Patient Safety
SAE	serious adverse event
SOP	Standard Operating Procedure
SS	Safety Set
SV	Screening Visit
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	Unscheduled Visit
VNS	vagal nerve stimulation
YEV	Yearly Evaluation Visit

1 SUMMARY

EP0085 is an open-label, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam (BRV) used as adjunctive treatment in subjects ≥16 years with partial seizures with or without secondary generalization. The primary objective is to evaluate the long-term safety and tolerability of BRV in focal epilepsy subjects with partial seizures. The secondary objective is to evaluate the maintenance of efficacy of BRV over time.

The subject population will be subjects with partial seizures with or without secondary generalization. Subjects of a minor age are included only where legally permitted and ethically accepted.

Rollover subjects from EP0083 must complete the Treatment and Transition Period of EP0083 prior to enrollment into EP0085. Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter into this study.

In addition, for accumulating safety data, subjects in Japan that have well-characterized focal epilepsy with seizures that are uncontrolled in spite of treatment with at least 1 permitted anti-epileptic drug (AED), having experienced 1 to <8 partial seizures within the 8 weeks prior to BRV administration may be directly enrolled.

Directly enrolled subjects and subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment. Subjects from N01379 can enter EP0085 at a dose up to 200mg/day.

The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered in equal morning and evening doses except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study medication in the last week of down-titration is given only in the morning.

Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

The primary safety variable is treatment-emergent adverse events (TEAEs). Other safety variables include safety laboratory tests (blood chemistry, hematology, and urinalysis), vital signs, body weight, electrocardiograms (ECGs), physical and neurological examinations.

Efficacy variables for rollover subjects include:

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

- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

Efficacy variables for directly enrolled subjects in Japan include:

- Percent reduction in partial seizure frequency per 28 days from 8 weeks prior to BRV administration to the Evaluation Period
- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure frequency from 8 weeks prior to BRV administration
- Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized, and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

Overall, approximately 217 subjects are planned for enrollment. In Japan, it is estimated that approximately 127 subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 (approximately 90 subjects) or enroll from N01379 sites in Japan (7 subjects) and the plan that 30 Japanese subjects will be directly enrolled in this study. Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083 (approximately 90 subjects).

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 16.1]).

Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAE-publication (ILAE, 1989, Appendix 2 [Section 16.2]).

2.2 Background information regarding product

Brivaracetam is a chemical relative of the AED levetiracetam (LEV [Keppra®/E-Keppra®]). Like LEV, BRV displays a high and selective interaction with a novel brain-specific binding site synaptic vesicle protein 2A (SV2A). 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 pharmacokinetics (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 cytochrome P450 (CYP)2C19 (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 CYP3A4 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 (3.0µg/mL) at BRV doses of 100 and 150mg/day.

2.3 Efficacy with BRV in long-term follow-up studies in subjects with partial seizure

Subjects who completed 1 of the primary efficacy studies (N01358, N01252, or N01253) or 1 of the supporting efficacy studies (N01114, N01193, or N01254) had the option to participate in open-label extension studies (N01125, N01199, and N01379) to further evaluate the safety and efficacy of BRV. In the long-term follow-up (LTFU) studies, in which physicians could increase or decrease BRV doses as needed, modal doses of 100mg/day, 150mg/day, and 200mg/day were reported for 22.4%, 46.5%, and 14.7% of subjects with ≥12 months exposure, respectively. Similar findings were reported for subjects with ≥24 months exposure.

The long-term follow-up studies indicate a consistently high percentage of subjects continued to receive BRV and clinically relevant efficacy was maintained over time across all regions.

2.4 Safety with BRV

In the BRV clinical development program, 3970 subjects were 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 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 placebo (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 is being evaluated in 5 ongoing LTFU studies in adults (N01125, N01199, N01315, N01379, and N01372). The safety profile in the open-label extension studies (up to 8 years) was consistent to that observed in the short-term, placebo-controlled studies.

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

2.5 Rationale for the study

EP0085 will explore the long-term safety and efficacy of BRV in subjects in Japan and China. EP0085 will include subjects who have completed EP0083, Japanese subjects from N01379, and directly enrolled Japanese subjects.

The proposed study is intended to provide evidence of the long-term safety and efficacy of BRV as adjunctive therapy in subjects with partial seizures. In alignment with the doses previously assessed in the feeder studies, doses of BRV 50 to 200mg/day will be assessed in EP0085. EP0083 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in subjects (≥16 to 80 years of age) with partial seizures

with or without secondary generalization. N01379 is an open-label, multicenter, long-term follow up study for N01358 which is the pivotal global efficacy study for BRV used as adjunctive treatment in adult subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. For sites in Japan, subjects with uncontrolled seizures treated by at least 1 permitted concomitant AED may be directly enrolled in order to provide additional safety and efficacy data with BRV.

3 STUDY OBJECTIVES

3.1 Primary objective

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

3.2 Secondary objective

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

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variable is TEAEs.

4.1.2 Other safety variables

The other safety variables are as follows:

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

4.1.3 Efficacy variables

The efficacy variables for rollover subjects include:

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

Efficacy variables for directly enrolled subjects in Japan include:

- Percent reduction in partial seizure frequency per 28 days from 8 weeks prior to BRV administration to the Evaluation Period
- Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure frequency from 8 weeks prior to BRV administration
- Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized, and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period

5 STUDY DESIGN

5.1 Study description

EP0085 is a Phase 3, open-label, LTFU, multicenter, noncomparative, and dose flexible study to be conducted in Japan and China. The population will be subjects (≥16 years of age) with partial seizures with or without secondary generalization. Subjects of a minor age are included only where legally permitted and ethically accepted. In Japan, subjects meeting the inclusion and exclusion criteria as specified in Section 6.1 may be directly enrolled. Rollover subjects must complete the Treatment and Transition Period of EP0083 prior to enrollment into EP0085.

In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, may enter this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Directly enrolled subjects in Japan and rollover subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment.

Japanese subjects from N01379 can enter EP0085 at a dose up to 200mg/day. After Visit 1, the next visit for subjects entering from N01379 will be Visit 4 (Visit 2 and Visit 3 will not be conducted). Subsequent visits will be conducted according to the visit schedule provided in Table 5–3. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered as a symmetrical morning and evening dose except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study medication in the last week of down-titration is given only in the morning.

5.1.1 Study duration per subject

The following study periods are defined:

- Screening Visit (Visit 0, up to 3 weeks before the Entry Visit (EV) for direct enrollers in Japan only)
- Evaluation Period (Visit 1 to End of Study Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in EP0083 and N01379 will enter the Evaluation Period.
- Down-Titration Period (up to 4 weeks)
  - If the subject is discontinuing study drug, the Investigator will first plan an EDV followed by the progressive down-titration of study drug.
  - During the Down-Titration Period, the BRV dose may be decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 25mg/day for 1 week should be included prior to the 2-week Study Drug-Free Period.
- 2-week Study Drug-Free Period: After completion of the Down-Titration Period, or for those subjects who for extenuating circumstances do not complete a Down-Titration Period, the subject will be required to enter a 2-week Study Drug-Free Period, followed by a Final Visit (FV).

Visits should occur on the specified Visit/Week. A ±7 day window for each specified Visit/Week is allowed, provided the subject has adequate investigational medicinal product (IMP) to sustain the visit window. The end of the study is defined as the date of the last visit of the last subject in the study.

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

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

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

5.1.2 Planned number of subjects and sites

Overall, approximately 217 subjects are planned for enrollment. In Japan, it is estimated that approximately 127 subjects will enter the study. This estimate assumes that at least 90% of randomized Japanese subjects will complete EP0083 (approximately 90 subjects) or enroll from N01379 sites in Japan (7 subjects) and the plan that 30 Japanese subjects will be directly enrolled in this study.

In China Mainland, it is estimated that approximately 90 subjects will enter the study, based on the assumption that at least 90% of randomized Chinese subjects will complete EP0083.

It is estimated that approximately 50 Japan sites and 25 China Mainland sites will participate in the study.

5.1.3 Anticipated regions and countries

The study is planned to be conducted in Japan and China Mainland.

5.2 Schedule of study assessments

The schedule of study assessments for subjects transitioning from EP0083 and N01379 is provided in Table 5–1. The schedule of study assessments for subjects directly enrolled into EP0085 in Japan is provided in Table 5-2.

Table 5–1: Schedule of study assessments for subjects transitioning from EP0083 and N01379

Assessments	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V1**	**V2[a], V4, V6, V8, V10⋯**	**V3[a], V5, V9⋯**	**V7, V11⋯**	**NA**	**NA**
Month	**M0**	**M1, M3, M9, M15, M21⋯**	**M2, M6, M18⋯**	**M12, M24⋯**	**NA**	**NA**
Week	**W0**	**W4, W12, W36, W60, W84⋯**	**W8, W24, W72⋯**	**W48, W96⋯**	**NA**	**NA**
Written informed consent	X[b]					
Subject identification card dispensed	X					
Eligibility assessment	X					
Demography	X					
Medical/procedures history	X[c]					
Epilepsy history	X[c]					
AED history	X[c]					
Vital signs	X*	X	X	X	X	X
Body weight and height[d]	X*[d]	X	X	X	X	X
Physical examination	X*		X	X	X	X
Neurological examination	X*		X	X	X	X
12-lead ECG[e]	X*		X	X	X	X
IVRS/IWRS	X	X	X	X	X	X
Subject's DRC dispensed	X	X	X	X	X	

Table 5–1: Schedule of study assessments for subjects transitioning from EP0083 and N01379

Assessments	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V1**	**V2[a], V4, V6, V8, V10…**	**V3[a], V5, V9…**	**V7, V11…**	**NA**	**NA**
Month	**M0**	**M1, M3, M9, M15, M21…**	**M2, M6, M18…**	**M12, M24…**	**NA**	**NA**
Week	**W0**	**W4, W12, W36, W60, W84…**	**W8, W24, W72…**	**W48, W96…**	**NA**	**NA**
Subject's DRC retrieval		X	X	X	X	X
Seizure counts[f]	X*	X	X	X	X	X
Laboratory safety assessments[g]	X*	X[e]	X	X	X	X[g]
Pregnancy test[h]	X*	X	X	X	X	X
AE reporting	X*	X	X	X	X	X
C-SSRS	X*	X	X	X	X	X
Medical procedures	X*	X	X	X	X	X
Concomitant AEDs	X*	X	X	X	X	X
Concomitant non-AEDs	X*	X	X	X	X	X
Study drug dispensing	X	X	X	X	X	
Study drug return/accountability		X	X	X	X	X
End of study status[i]					X	X

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; C-SSRS=Columbia-Suicide Severity Rating Scale; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; IVRS=interactive voice response system; IWRS= interactive web response system; M=Month; MEV=Minimal Evaluation Visit; NA=not applicable; V=Visit; W=week; YEV= Yearly Evaluation Visit

Table 5–1: Schedule of study assessments for subjects transitioning from EP0083 and N01379

Assessments	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V1**	**V2[a], V4, V6, V8, V10⋯**	**V3[a], V5, V9⋯**	**V7, V11⋯**	**NA**	**NA**
Month	**M0**	**M1, M3, M9, M15, M21⋯**	**M2, M6, M18⋯**	**M12, M24⋯**	**NA**	**NA**
Week	**W0**	**W4, W12, W36, W60, W84⋯**	**W8, W24, W72⋯**	**W48, W96⋯**	**NA**	**NA**

Note: For subjects who have completed EP0083 or N01379, assessments marked (*) should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1.

[a] After Visit 1, for subjects entering from N01379 V2 and V3 will not be conducted. Subsequent visits will be conducted according to the visit schedule provided in Table 5–3.

[b] Informed consent must be obtained during the previous study.

[c] General medical and procedures history, AED history, and epilepsy history will be obtained from the Baseline of EP0083 or Baseline of N01358 (for subjects entering from N01379) and do not need to be recorded on the eCRF for this study.

[d] Height will be recorded at V1 only.

[e] At the FV, a 12-lead ECG is mandatory, except if the FV follows an EDV where ECG results were normal.

[f] Seizure counts are collected on the subject's daily record card on a daily basis.

[g] Laboratory safety assessment will not be performed at MEV. Only liver function tests will be performed at the MEV in Visit 4 (M3) and Visit 6 (M9). Laboratory safety assessment is mandatory at the FV, except if the FV follows an EDV where laboratory results were normal. The result of the calculated creatinine clearance will be provided by the central laboratory.

[h] A urine pregnancy test will be done for female subjects with childbearing potential.

[i] End of study status will be completed at the FV for subjects having performed an EDV and down-titration of BRV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects). Alternatively, end of study status will be completed at the End of Study Visit for subjects who will be converted without down-titration to commercial BRV if, when, and where available.

Table 5-2: Schedule of study assessments for subjects directly enrolled into EP0085 in Japan

Assessments	SV	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V0**	**V1**	**V2, V4, V6, V8, V10…**	**V3, V5, V9…**	**V7, V11…**	**NA**	**NA**
Month	**-**	**M0**	**M1, M3, M9, M15, M21…**	**M2, M6, M18…**	**M12, M24…**	**NA**	**NA**
Week	**(-2 to -21 days)**	**W0**	**W4, W12, W36, W60, W84…**	**W8, W24, W72…**	**W48, W96…**	**NA**	**NA**
Written informed consent	X						
Subject identification card dispensed	X						
Eligibility assessment	X	X					
Demography	X						
Medical/procedures history	X						
Epilepsy history	X						
AED history	X						
Birth control	X						
Vital signs	X	X	X	X	X	X	X
Body weight and height[a]	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X
Neurological examination	X			X	X	X	X
12-lead ECG[b]	X			X	X	X	X
EEG[c]	X						

Table 5-2: Schedule of study assessments for subjects directly enrolled into EP0085 in Japan

Assessments	SV	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V0**	**V1**	**V2, V4, V6, V8, V10…**	**V3, V5, V9…**	**V7, V11…**	**NA**	**NA**
Month	**-**	**M0**	**M1, M3, M9, M15, M21…**	**M2, M6, M18…**	**M12, M24…**	**NA**	**NA**
Week	**(-2 to -21 days)**	**W0**	**W4, W12, W36, W60, W84…**	**W8, W24, W72…**	**W48, W96…**	**NA**	**NA**
Neuro-imaging procedure[d]	X						
IVRS/IWRS	X	X	X	X	X	X	X
Subject's DRC dispensed		X	X	X	X	X	
Subject's DRC retrieval			X	X	X	X	X
Seizure counts[e]	X	X	X	X	X	X	X
Laboratory safety assessments[f]	X	X	X	X	X	X	X[f]
Pregnancy test[g]	X	X	X	X	X	X	X
AE reporting	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X
Medical procedures	X	X	X	X	X	X	X
Concomitant AEDs[h]	X	X	X	X	X	X	X
Concomitant non-AEDs	X	X	X	X	X	X	X
Study drug dispensing		X	X	X	X	X	
Study drug return/accountability			X	X	X	X	X

Table 5-2: Schedule of study assessments for subjects directly enrolled into EP0085 in Japan

Assessments	SV	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V0**	**V1**	**V2, V4, V6, V8, V10…**	**V3, V5, V9…**	**V7, V11…**	**NA**	**NA**
Month	**-**	**M0**	**M1, M3, M9, M15, M21…**	**M2, M6, M18…**	**M12, M24…**	**NA**	**NA**
Week	**(-2 to -21 days)**	**W0**	**W4, W12, W36, W60, W84…**	**W8, W24, W72…**	**W48, W96…**	**NA**	**NA**
End of study status[i]						X	X

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; C-SSRS=Columbia-Suicide Severity Rating Scale; DE=Direct Enrollment; DRC=daily record card; ECG=electrocardiogram; eCRF=electronic case report form; EDV=Early Discontinuation Visit; EEG=electroencephalogram; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; IVRS=interactive voice response system; IWRS= interactive web response system; M=Month; MEV=Minimal Evaluation Visit; NA=not applicable; SV=Screening Visit; V=Visit; W=week; YEV= Yearly Evaluation Visit

Note: Other than the SV and EV, the same study assessment will be performed at subsequent visits for all subjects. Subsequent visits will be conducted according to the visit schedule provided in Table 5–3.

[a] Height will be recorded at the SV only.

[b] At the FV, a 12-lead ECG is mandatory, except if the FV follows an EDV where ECG results were normal.

[c] If no appropriate EEG result (within the last 10 years) is available, the EEG must be scheduled at the SV and the results received before the EV.

[d] A neuro-imaging procedure (brain magnetic resonance imaging/brain computerized tomography scan or any other imaging test) should be performed if no report is available within the previous 2 years. If there is no a known history and clinical signs or suspicion of brain tumor, performing a neuro-imaging procedure for the purpose of the study is not mandatory. If the investigator can judge a participant's eligibility by his/her own medical judgement without performing neuro-imaging procedure, it is also acceptable. However, if the etiology of epilepsy is a brain tumor, or the participant has any intracranial structural abnormality as documented by a previous neuro-imaging procedure, the participant needs to have documentation of a neuro-imagining procedure which is no older than 2 years.

[e] At the SV and EV (For DE), historical seizure information (including type, frequency, and date) should be checked. Historical seizure information must have been prospectively recorded on a subject's own document (eg, DRC). After the EV, seizure counts are collected on the subject's DRC on a daily basis

[f] Laboratory safety assessment will not be performed at MEV. Only liver function tests will be performed at the MEV in Visit 4 (M3) and Visit 6 (M9). Laboratory safety assessment is mandatory at the FV, except if the FV follows an EDV where laboratory results were normal. The result of the calculated creatinine clearance will be provided by the central laboratory.

[g] At the SV, a serum pregnancy test will be performed for female subjects with childbearing potential. At all subsequent visits, a urine pregnancy test will be performed

[h] Concomitant levetiracetam is permitted for directly enrolled subjects in Japan, but not allowed for subjects transitioning from EP0083 and N01379.

Table 5-2: Schedule of study assessments for subjects directly enrolled into EP0085 in Japan

Assessments	SV	EV	MEV	FEV	YEV	End of Study Visit or EDV	FV
Visit	**V0**	**V1**	**V2, V4, V6, V8, V10…**	**V3, V5, V9…**	**V7, V11…**	**NA**	**NA**
Month	**-**	**M0**	**M1, M3, M9, M15, M21…**	**M2, M6, M18…**	**M12, M24…**	**NA**	**NA**
Week	**(-2 to -21 days)**	**W0**	**W4, W12, W36, W60, W84…**	**W8, W24, W72…**	**W48, W96…**	**NA**	**NA**

[i] End of study status will be completed at the FV for subjects having performed an EDV and down-titration of BRV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects). Alternatively, end of study status will be completed at the End of Study Visit for subjects who will be converted without down-titration to commercial BRV if, when, and where available.

5.3 Schematic diagram

A full visit schedule is presented in Table 5–3.

Table 5–3: Full visit schedule

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

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

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

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

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

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

5.4 Rationale for study design and selection of dose

Directly enrolled subjects and subjects from EP0083 will be started on a BRV dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment. Subjects who entered from N01379 can enter EP0085 at a dose up to 200mg/day. The BRV 50 to 200mg/day is approved as the effective dose of BRV for adults in EU/US without titration. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered in equal morning and evening doses except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study medication in the last week of down-titration is given only in the morning.

In Phase 2/3 studies for partial seizures with BRV doses up to 200mg/day, BRV had a low dropout rate and was generally well tolerated. The most frequently reported TEAEs were headache, somnolence, dizziness, and fatigue. The starting dose of BRV 100mg/day was selected from N01358 efficacy results that were numerically similar between 100 and 200mg/day, and the starting dose in US and EU labeling. The BRV dose can be adjusted based on the individual subject's seizure control and/or tolerability after the first 2 weeks, up to a maximum dose of BRV 200mg/day.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Eligibility criteria in Japan

6.1.1 Inclusion criteria for all subjects

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

1. An IRB/IEC approved written informed consent signed and dated by the subject or by parent(s) or legally representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Male/female subject from 16 years of age or older. Subjects who are not legal adults may only be included where legally permitted and ethically accepted.
4. Subject for whom the Investigator believes a reasonable benefit from the long-term administration of BRV may be expected.
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. Subject/legally representative considered as reliable and capable of adhering to the protocol (eg, able to understand and complete diaries and questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

6.1.2 Additional inclusion criteria for rollover subjects

In addition to the inclusion criteria for all subjects in Japan (Section 6.1.1), the following criteria must also be met for rollover subjects in Japan:

3. Subject completed the Treatment Period and Transition Period of EP0083 or is ongoing in N01379 sites in Japan.

6.1.3 Additional inclusion criteria for directly enrolled subjects

In addition to the inclusion criteria for all subjects in Japan (Section 6.1.1), the following criteria must also be met for directly enrolled subjects in Japan:

7. Subject has a body weight ≥40kg at the Screening Visit (SV).
8. Subject has well-characterized focal epilepsy/epileptic syndrome according to the 1989 ILAE classification.
9. Subject has had an electroencephalogram (EEG) reading compatible with the clinical diagnosis of focal epilepsy within the last 10 years. If there is no appropriate EEG available within the last 10 years, a Baseline EEG must be scheduled at the SV and the results received before the EV.
10. Subject has 1 to <8 partial seizures (according to the 1981 ILAE classification) during the 8 weeks prior to BRV administration.
11. Subject's seizures are uncontrolled while treated by at least 1 permitted concomitant AED. Vagal nerve stimulation (VNS) will be allowed and counted as a concomitant AED.

6.1.4 Exclusion criteria for all subjects

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

1. Subject has developed hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol during the course of the core study.
2. Severe medical, neurological or psychiatric disorders, or laboratory values which may have an impact on the safety of the subject.
4. Planned participation in any other clinical study of another investigational drug or device during this study.
5. Pregnant or lactating woman.
6. Any medical condition which, in the Investigator's opinion, warrants exclusion.

6.1.5 Additional exclusion criteria for rollover subjects

In addition to the exclusion criteria for all subjects in Japan (Section 6.1.4), the following exclusion criteria also apply for rollover subjects in Japan:

3. Poor compliance with the visit schedule or medication intake in the previous BRV studies.
7. 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 C-SSRS at the Entry Visit (EV).
8. Subject has >2xULN of any of the following at the EV: ALT, AST, 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%).

6.1.6 Additional exclusion criteria for directly enrolled subjects

In addition to the exclusion criteria for all subjects in Japan (Section 6.1.4), the following exclusion criteria also apply for directly enrolled subjects in Japan:

9. 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).
10. 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 C-SSRS at the SV.
11. Subject has >2xULN of any of the following at the SV: ALT, AST, 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 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.
12. Subject previously enrolled in this study or any other prior study with BRV as a dosing arm.
13. Subject has experienced febrile seizures exclusively. The occurrence of febrile seizures in addition to other unprovoked seizures is not exclusionary.
14. Subject/legal representative is not able to read and understand the Informed Consent form (ICF), Assent form, or daily record card (DRC) instructions.
15. Subject has a history or presence of status epilepticus during the 30 days preceding the SV.

16. Subject has a history or presence of known psychogenic nonepileptic seizures.
17. Study participant has been treated with vigabatrin and has visual field defects.
18. Subject is 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 the SV.
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 per investigator assessment. Stable arteriovenous malformations, meningiomas, or other benign tumors may be acceptable.
20. Subject has any clinical conditions (eg, bone marrow suppression, severe renal impairment) which, per investigator discretion, impair reliable participation in the study or necessitate the use of medication not allowed by protocol.
21. Subject has the presence of a terminal illness.
22. Subject has the presence of a serious infection.
23. 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 Investigator.
24. Subject has clinically significant ECG abnormalities according to the Investigator.
25. Subject has known alcohol or drug addiction or abuse within the last 2 years.

6.2 Eligibility criteria in China

6.2.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent signed and dated by the subject or by parent(s) or legally representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Male/female subject from 16 years of age or older. Subjects who are not legal adults may only be included where legally permitted and ethically accepted.
3. Subject completed the Treatment Period and Transition Period of EP0083.
4. Subject for whom the Investigator believes a reasonable benefit from the long-term administration of BRV may be expected.
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. Subject/legally representative considered as reliable and capable of adhering to the protocol (eg, able to understand and complete diaries and questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

6.2.2 Exclusion criteria

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

1. Subject has developed hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol during the course of the core study.
2. Severe medical, neurological or psychiatric disorders, or laboratory values which may have an impact on the safety of the subject.
3. Poor compliance with the visit schedule or medication intake in the previous BRV studies.
4. Planned participation in any other clinical study of another investigational drug or device during this study.
5. Pregnant or lactating woman.
6. Any medical condition which, in the Investigator's opinion, warrants exclusion.
7. 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 the EV.
8. Subject has >2 x upper limit of normal (ULN) of any of the following at the EV: 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%).

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.
- In the event of a suicide attempt, the subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

  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 or discontinuation. The Investigator should make 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 or discontinuation.

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 10.2.1. 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 TREATMENTS

7.1 Description of investigational medicinal products

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

7.2 Treatments to be administered

Directly enrolled subjects in Japan and subjects rolling over from EP0083 will be started on a BRV dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment.

Subjects from Japan who entered from N01379 can enter EP0085 at a dose up to 200mg/day. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered in equal morning and evening doses except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day.

For all subjects, the first intake of study medication should occur in the evening of the day of the EV. Subjects should take tablets according to instructions provided by the Investigator.

During the Down-Titration Period, the BRV dose may be decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 25mg/day for 1 week should be included prior to the 2-week Study Drug-Free Period. The subject will be required to enter a 2-week Study Drug-Free Period for 2 weeks, followed by a FV.

7.3 Packaging

Brivaracetam tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice 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 reconciled and 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 will be supplied to the subject/parent(s)/legal representative(s) at protocol specified time points provided in Table 5–1 and Table 5-2).

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 subject/parent(s)/legal representative(s) must record the situation of medication compliance every time the subject takes 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 medications/treatments

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 EV 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)

At the beginning of EP0085, the concomitant AEDs that were used in EP0083 and N01379 are permitted for rollover subjects. Subjects directly enrolled into EP0085 in Japan will enter the study receiving at least 1 permitted concomitant AED.

The investigator (or designee) will be allowed to change the type, dosage and administration, or discontinuation/resumption of concomitant AEDs to optimize tolerability and seizure reduction for each subject. Antiepileptic drugs (Appendix 3 [Section 16.3]) are permitted during the study. Changes in concomitant AEDs will be allowed only if the dose of BRV has been stable for the previous 4 weeks; BRV dose must remain stable during changes to concomitant AEDs. New AEDs may be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of BRV. The concomitant AEDs can be carefully tapered or discontinued at the discretion of the investigator.

Monotherapy with BRV is permitted. Increasing the dose of BRV and/or concomitant AEDs, as well as addition of a new AED should be done at a visit (scheduled or unscheduled). There are no restrictions for concomitant AEDs during the Taper Period, considering subject safety.

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

7.8.2 Prohibited concomitant treatments (medications and therapies)

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

- BRV (other than IMP)
- LEV (LEV is not prohibited for directly enrolled subjects in Japan)
- 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 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. 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.

7.9 Blinding

This is an open-label LTFU study of the preceding double-blind study EP0083 and open-label study N01379, thus, subjects are not blinded.

7.10 Randomization and numbering of subjects

Since EP0085 is an open-label LTFU study for EP0083 and open-label study N01379, subjects will not be randomized to any treatment groups. Subjects from EP0083 will start with a dose of BRV 100mg/day (2 equally divided doses administered twice daily) and will be maintained on that dose for at least 2 weeks, unless they are unable to tolerate the dose. Subjects from Japan who participated in N01379 can enter EP0085 at a dose up to 200mg/day.

Subjects from EP0083 and N01379 will continue with the 5-digit subject numbers assigned by the IVRS/IWRS in the preceding studies. Directly enrolled subjects will receive a 5-digit number assigned by the IVRS/IWRS at Screening that serves as the subject identifier throughout the study.

8 STUDY PROCEDURES BY VISIT

Prior to any study activities, the subject/parent(s)/legal representative(s) will be asked to read and sign an ICF that has been approved by an IRB/IEC and which complies with regulatory requirements. The subject/parent(s)/legal representative(s) 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, the subject/parent(s) or legal representative(s) will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study. Additionally, if applicable (according to subject's age and local requirements), the subject will sign an IRB/IEC-approved Assent form.

8.1 Screening Visit (for direct enrollers in Japan only)

The following tasks and procedures are to be performed between Day -21 and Day -2, prior to Visit 1 (EV) for direct enrollers in Japan:

- Written informed consent
- Subject identification card dispensed
- Eligibility assessment
- Demography
- Medical/procedures history
- Epilepsy history
- AED history
- Birth control
- Vital signs
- Body weight
- Height
- Physical examination
- Neurological examination
- 12-lead ECG
- EEG (if no EEG result within the previous10 years is available)
- Neuro-imaging procedure (per Investigator discretion)
- IVRS/IWRS
- Seizure counts (prospectively recorded historical seizure information)
- Laboratory safety assessments including hematology, blood chemistry, and urinalysis
- Serum pregnancy test
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AEDs
- Concomitant non-AEDs

8.2 Entry Visit (for direct enrollers in Japan only)

The EV assessments for direct enrollers in Japan are as follows:

- Eligibility assessment
- Vital signs
- Body weight
- IVRS/IWRS

- Subject's daily record card (DRC) dispensed
- Seizure counts (prospectively recorded historical seizure information)
- Laboratory safety assessments including hematology, blood chemistry, urinalysis and urine pregnancy test (if applicable)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AEDs
- Concomitant non-AEDs
- Study drug dispensing

8.3 Entry Visit (rollovers from China and Japan)

The following tasks and procedures are to be performed at this visit (for subjects who have completed EP0083 and N01379, assessments marked [*] should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1).

The EV assessments are as follows:

- Written informed consent (must be obtained during the previous study)
- Subject identification card dispensed
- Eligibility assessment
- Demography
- Vital signs*
- Body weight*
- Height
- Physical examination*
- Neurological examination*
- 12-lead ECG*
- IVRS/IWRS
- Subject's daily record card (DRC) dispensed
- Seizure counts*
- Laboratory safety assessments including hematology, blood chemistry, urinalysis and urine pregnancy test (if applicable)*
- AE reporting*
  - Ongoing AEs at the time of subject completion of EP0083 or N01379 will be obtained from the database for EP0083 or N01379 and should not be recorded on the eCRF for

EP0085, unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the eCRF for EP0085 with the onset date corresponding to the date of change in condition.

- C-SSRS*
- Medical procedures*
- Concomitant AEDs*
  - Ongoing medications (AEDs and non-AEDs) at the time of subject completion of EP0083 or N01379 will be obtained from the database for EP0083 or N01379 and should not be recorded on the eCRF for EP0085, unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the eCRF for EP0085 with the start date corresponding to the date of change in administration.
- Concomitant non-AEDs*
- Study drug dispensing

The following data will be obtained from the Baseline of EP0083 or N01358 (for subjects entering from N01379) and do not need to be recorded on the eCRF for this study.

- General medical and procedures history
- AED history
- Epilepsy history.

8.4 Minimal Evaluation Visits (all subjects)

After V1 for subjects entering from N01379, V2 will not be conducted). Subsequent visits will be conducted according to the visit schedule provided in Table 5–3.

At the Minimal Evaluation Visits (MEV) assessments are as follows:

- Vital signs
- Body weight
- IVRS/IWRS
- Subject's DRC dispensed
- Subject's DRC retrieval
- Seizure counts (collected on the subject's DRC on a daily basis)
- Urine pregnancy test (if applicable)
- Liver function tests will be performed in V4 (M) and V6 (M 9) as described in Section 10.2.
- AE reporting
- C-SSRS
- Medical procedures

- Concomitant AEDs
- VNS settings
- Concomitant non-AEDs
- Study drug dispensing
- Study drug return/accountability

8.5 Full Evaluation Visits (all subjects)

After V1 for subjects entering from N01379, V3 will not be conducted. Subsequent visits will be conducted according to the visit schedule provided in Table 5–2.

At the Full Evaluation Visits (FEV) assessments are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- 12-lead ECG
- IVRS/IWRS
- Subject's DRC dispensed
- Subject's DRC retrieval
- Seizure counts (collected on the subject's DRC on a daily basis)
- Laboratory safety assessments including hematology, blood chemistry, urinalysis and urine pregnancy test (if applicable)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AEDs
- VNS settings
- Concomitant non-AEDs
- Study drug dispensing
- Study drug return/accountability

8.6 Yearly Evaluation Visit (all subjects)

At the Yearly Evaluation Visit (YEV) assessments are as follows:

- Vital signs
- Body weight

- Physical examination
- Neurological examination
- 12-lead ECG
- IVRS/IWRS
- Subject's DRC dispensed
- Subject's DRC retrieval
- Seizure counts (collected on the subject's DRC on a daily basis)
- Laboratory safety assessments including hematology, blood chemistry, urinalysis and urine pregnancy test (if applicable)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AEDs
- VNS settings
- Concomitant non-AEDs
- Study drug dispensing
- Study drug return/accountability

8.7 End of Study Visit or Early Discontinuation Visit (all subjects)

At the End of Study Visit or Early Discontinuation Visit (EDV) assessments are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- 12-lead ECG
- IVRS/IWRS
- Subject's DRC dispensed
- Subject's DRC retrieval
- Seizure counts (collected on the subject's DRC on a daily basis)
- Laboratory safety assessments including hematology, blood chemistry, urinalysis and urine pregnancy test (if applicable)
- AE reporting
- C-SSRS

- Medical procedures
- Concomitant AEDs
- VNS settings
- Concomitant non-AEDs
- Study drug dispensing
- Study drug return/accountability
- End of study status (end of study status will be completed at the End of Study Visit for subjects who will be converted without down-titration to commercial BRV if, when, and where available).

8.8 Final Visit (all subjects)

At the Final Visit (FV) assessments are as follows:

- Vital signs
- Body weight
- Physical examination
- Neurological examination
- 12-lead ECG (mandatory, except if the FV follows an EDV where ECG results were normal)
- IVRS/IWRS
- Subject's DRC retrieval
- Seizure counts (collected on the subject's DRC on a daily basis)
- Laboratory safety assessments (mandatory, except if the FV follows an EDV where laboratory results were normal): hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- AE reporting
- C-SSRS
- Medical procedures
- Concomitant AEDs
- VNS settings
- Concomitant non-AEDs
- Study drug return/accountability
- End of study status

The FV is not applicable to subjects who convert to commercial BRV (if, when, and where available).

8.9 Unscheduled Visit (all subjects)

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 (UV) is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If a UV 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.

9 ASSESSMENT OF EFFICACY

Efficacy variables will be assessed using the seizure count information recorded on the DRC.

At each visit, the subject will receive a DRC, to be filled in on days on which a seizure occurs, and to be returned at the next visit. No DRC will be dispensed at the UV or the FV.

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 IMP, 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, healthcare provider consultations not foreseen per protocol, and AEs will be reported by the Investigator on the specific pages of the eCRF.

The DRC will be considered as source documentation. 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.

9.1 Additional efficacy measures

9.1.1 Medical procedures

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.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 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 ICF), 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.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

10.1.1.2 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 10.1.1.3], 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.)

10.1.1.3 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 10.1.2.3).

The following Preferred Terms are considered as 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.

10.1.2 Procedures for reporting and recording AEs

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.

10.1.2.1 Description of AEs

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

10.1.2.2 Rule for repetition of an AE

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

10.1.2.3 Additional procedures for reporting SAEs

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.

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.

10.1.3 Follow up of AEs

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 10.2.1.4 .

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.

10.1.4 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 early discontinuation visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the early discontinuation visit.
- A Safety Follow-Up 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/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 an 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.

10.1.5 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.

10.1.6 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).

10.1.7 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.

10.2 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 4.5mL by sampling, which includes 2mL for hematology and 2.5mL for blood chemistry.

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

Table 10–1: 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; MEV=Minimal Evaluation Visits; 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. Liver function tests will be assessed at MEVs (Visit 4 and Visit 6) during the first year in addition to the full laboratory assessments described in Section 8.

[b] Includes bacteria, cells, casts, and crystals for all samples.

The creatinine clearance (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.

For rollover subjects in China and Japan, laboratory safety assessments at the EV will be taken from the last visit of EP0083 or N01379 and do not need to be recorded on the eCRF. Laboratory safety assessments will be performed at time points specified in the schedules of study

assessments (Table 5–1 and Table 5-2). In addition, liver function tests will be performed at MEVs (Visit 4 and Visit 6) during the first year. Laboratory assessments will also be mandatory at the FV, except if the FV follows an EDV where laboratory results were normal.

Where applicable, females of childbearing potential), a blood pregnancy test (beta-human chorionic gonadotropin 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 pregnancy tests will be provided by fax to the Investigator within 72 hours after sample receipt.

10.2.1 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 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.2.1.1). 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 10.2.1.4).

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 10–2 summarizes the approach to investigate PDILI.

Table 10–2: 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] 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 10.2.1.3); 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. 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 10.2.1.3).	

Table 10–2: 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 10.2.1.2). IMP discontinuation required if any of the following occur: Subject cannot comply with monitoring schedule. Liver chemistry values continue to increase. 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] Immediate IMP discontinuation required if: Liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without stabilization or evidence of resolution Continue to monitor until values normalize, stabilize, or return to within Baseline values[d]

Table 10–2: 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**

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 10.2.1.1 . 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.

10.2.1.1 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 subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed 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 10.2.1.3) and SAE report (if applicable).

10.2.1.2 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 10–2 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.

10.2.1.3 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 10–3 (laboratory measurements) and Table 10–4 (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 10–3: 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 10–4: 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: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • 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

10.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10–2. 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.

10.3 Other safety measurements

Other safety measurements include 12-lead ECGs, vital signs, physical examinations, neurological examination, body weight and height, and assessment of suicidality.

10.3.1 ECG

A standard 12-lead ECG will be performed at protocol specified time points according to the schedules of study assessments
(Table 5–1 and Table 5-2). For rollover subjects in China and Japan, data will be obtained from

the last visit of the previous study and should not be recorded in the eCRF at the EV. At the FV, a 12-lead ECG is mandatory for all subjects, except if the FV follows an EDV where ECG results were normal. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

The original 12-lead ECG tracing will be signed or initialed and dated by the Investigator and will be retained as part of the source data.

10.3.2 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 schedules of study assessments (Table 5–1 and Table 5-2).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF at the EV.

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

10.3.3 Physical examination

A standard physical examination will be performed at time points specified in the schedules of study assessments (Table 5–1 and Table 5-2).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF at the EV. Clinically significant new or worsened abnormalities will have to be reported as AEs.

10.3.4 Neurological examination

A standard neurological examination will be performed at time points specified in the schedules of study assessments (Table 5–1 and Table 5-2).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF at the EV. Clinically significant new or worsened abnormalities will have to be reported as AEs.

10.3.5 Body weight and height

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) will be measured at time points specified in the schedules of study assessments (Table 5–1 and Table 5-2).

For rollover subjects in China and Japan, height will be obtained from Visit 1 in EP0085. For direct enrollers in Japan, height will be obtained at the SV only.

10.3.6 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 schedules of study assessments (Table 5–1 and Table 5-2).

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 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.

11.2 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.

11.2.1 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.

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

11.2.2 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 11.2.1.

11.3 Data handling

11.3.1 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.

11.3.2 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. The data are entered into the eCRFs 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.

11.3.3 Subject Enrollment log/Subject Identification Code list

The subject's enrollment will be recorded in the Subject 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.

11.4 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.

11.5 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.

11.6 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).

11.7 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.

12 STATISTICS

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

For subjects from EP0083, subgroup analyses for Japanese and Chinese subjects will be conducted as well as analyses for the entire population.

Subjects from N01379 and direct enrollers from Japan will be analyzed separately.

12.1 Definition of analysis sets

Analysis populations will be defined as follows:

The Safety Set (SS) will consist of all subjects who took at least 1 dose of study medication.

The Full Analysis Set (FAS) will consist of all subjects who took at least 1 dose of study medication and have at least 1 seizure record on DRC during the Evaluation Period.

12.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Summary statistics will be presented for all subjects.

12.3 Planned efficacy analyses

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

The 28-day adjusted seizure frequency will be calculated by dividing the number of partial seizures by the number of days for which the DRC was completed and multiplying by 28.

Planned efficacy analyses for rollover subjects in China and Japan include:

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

Planned efficacy analyses for directly enrolled subjects in Japan include:

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

Planned efficacy analyses for all subjects (directly enrolled in Japan and rollovers in China and Japan) include:

- Seizure frequency per 28 days for partial seizures by 3-month periods over the Evaluation Period.
- Seizure frequency per 28 days for all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.
- Percentages of subjects continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period.

- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period.

12.4 Planned safety analyses

The long-term safety of BRV at individualized doses will be evaluated by means of the safety analyses. Summary tables will be presented over the Evaluation Period as well as Down-Titration Period for all subjects.

All safety variables will be analyzed by descriptive methods on the SS. Treatment-emergent adverse events will be summarized in incidence tables by Medical Dictionary for Regulatory Activities (MedDRA®) Primary System Organ Class and Preferred Term. Separate tables will be provided for AEs leading to withdrawal from the study and SAEs.

Laboratory values, vital signs, and weight will be summarized by period and visit. Possibly clinically significant treatment-emergent abnormalities for laboratory values, vital signs, and weight will be listed and summarized by period and visit. Electrocardiogram abnormalities will also be listed by period and visit.

12.5 Handling of protocol deviations

After all CRFs have been retrieved and entered and queries addressed, and prior to locking the clinical database a Data Evaluation Meeting (DEM) will be held. The purpose of this DEM will be to assess the quality of the data for subsequent database lock, identify protocol deviations, and finalize analysis populations.

12.6 Handling of dropouts or missing data

Safety and efficacy variables will be analyzed as they are available. Days with missing information will be ignored in the calculation of the seizure frequency.

Since subjects will drop out at different times from the study, results will be presented by overall and by 6 month periods.

12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned. However, data will be reported prior to the completion of this study to support regulatory submissions. At a minimum, 2 interim reports are planned after all ongoing subjects have completed Visit 5 (Week 24) and after all ongoing subjects have completed Visit 7 (Week 48). Regular monitoring of safety data collected during clinical studies will be performed by medically qualified Sponsor personnel or equivalent designee(s).

12.8 Determination of sample size

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

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 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 ICF 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 ICF. 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 ICF 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 ICF by the IRB/IEC and use of the amended form.

13.2 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.

13.3 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, ICF, IB, 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.

13.4 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).

13.5 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.

14 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.

15 REFERENCES

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16 APPENDICES

16.1 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)*

9. 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)

10. 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

11. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation)

12. 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)*

13. Simple partial onset followed by impairment of consciousness

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

b. With automatisms

14. 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.

16.2 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.

16.3 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

*Concomitant LEV is allowed only for direct enrollment participants. In that case, LEV is counted as 1 AED.

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 AEDs administered.

It is prohibited that subjects take BRV other than IMP, during the study.

16.4 Appendix 4 - Protocol Amendment 1

Rationale

This protocol has been amended to update descriptions in study duration per subject visit, treatments administered, and a few subject visits to provide a greater level of clarity.

In addition, minor administrative edits including typographical changes for formatting have been made.

Modifications and changes

Global changes

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

Specific changes

Change #1

LIST OF ABBREVIATIONS

The following abbreviation definitions were updated and corrected, respectively:

DEM	Data Evaluation Meeting
ILAE	International League Against Epilepsy

Change #2

Section 5.1.1 Study duration per subject

Additional text was added:

Visits should occur on the specified Visit/Week. A ±7 day window for each specified Visit/Week is allowed, provided the subject has adequate investigational medicinal product (IMP) to sustain the visit window.

Change #3

Table 5-1 Schedule of study assessments (EP0085)

For body weight and height at EV footnote (c) was added. For Laboratory safety assessments at MEV and FV footnote (e) was added.

Footnote (e)

[e] Laboratory safety assessment includes hematology, blood chemistry, and urinalysis. Liver function tests will be performed at the MEV in Visit 4 (M3) and Visit 6 (M9). Laboratory assessment will not be performed at MEV from the 2nd year, and is mandatory at the FV, except if the FV follows an EDV where laboratory results were normal.

Has been changed to:

[e] Laboratory assessment will not be performed at MEV. Only liver function tests will be performed at the MEV in Visit 4 (M3) and Visit 6 (M9). Laboratory safety assessment is mandatory at the FV, except if the FV follows an EDV where laboratory results were normal. The result of the calculated creatinine clearance will be provided by the central laboratory.

Footnote (g)

[g] End of study status will be completed at the FV for subjects having performed an EDV and down-titration of BRV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects). Alternatively, end of study status will be completed at the EDV for subjects who will be converted without down-titration to commercial BRV if, when, and where available.

Has been changed to:

[g] End of study status will be completed at the FV for subjects having performed an EDV and down-titration of BRV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects). Alternatively, end of study status will be completed at the End of Study Visit for subjects who will be converted without down-titration to commercial BRV if, when, and where available.

Change #4

Table 5-2 Full visit schedule

In the Visit column for V2 and V3 footnote (c) was added. In the Type of visit column to all MEV added footnote (b).

Footnote (b)

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

Has been changed to:

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

Change #5

Section 7.2 Treatments to be administered

During the Down-Titration Period, the BRV dose may be decreased in steps of a maximum of 50mg/day on a weekly basis. Subjects who are treating with BRV 50mg/day at the discontinuation decision by Investigator enter the 2-week Study Drug-Free Period after 1 week at 25mg/day. The subject will be required to enter a 2-week Study Drug-Free Period for 2 weeks, followed by a FV.

Has been changed to:

During the Down-Titration Period, the BRV dose may be decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 25mg/day for 1 week should be included prior to the 2-week Study Drug-Free Period. The subject will be required to enter a 2-week Study Drug-Free Period for 2 weeks, followed by a FV.

Change #6

Section 7.6 Drug accountability

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) preferably in the original package.

Has been changed to:

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 returned to UCB (or designee) preferably in the original package.

Change #7

Section 7.10 Randomization and numbering of subjects

Since EP0085 is an open-label LTFU study for EP0083, subjects will not be randomized to any treatment groups.

Has been changed to:

Since EP0085 is an open-label LTFU study for EP0083 and open-label study N01379, subjects will not be randomized to any treatment groups.

Change #8

Section 8.1 Entry visit

- AE reporting*

Ongoing AEs at the time of subject completion of EP0083 or N01379 will be obtained from the database for EP0083 or N01379 and should not be recorded on the eCRF for EP0085, unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the eCRF for N01379 with the onset date corresponding to the date of change in condition.

Has been changed to:

- AE reporting*

Ongoing AEs at the time of subject completion of EP0083 or N01379 will be obtained from the database for EP0083 or N01379 and should not be recorded on the eCRF for EP0085, unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the eCRF for EP0085 with the onset date corresponding to the date of change in condition

Change #9

Section 8.2 Minimal Evaluation Visits

The following assessment was added:

- Urine pregnancy test (if applicable)

The following text was removed:

Laboratory safety assessments including hematology, blood chemistry, urinalysis and urine pregnancy test (if applicable);

Change #10

Section 8.3 Full Evaluation Visits

The following assessment was removed:

- Mental and psychiatric status

Change #11

Section 8.5 End of study Visit or Early Discontinuation Visit

End of study status (end of study status will be completed at the EDV for subjects who will be converted without down-titration to commercial BRV if, when, and where available).

Has been changed to:

End of study status (end of study status will be completed at the End of Study Visit for subjects who will be converted without down-titration to commercial BRV if, when, and where available).

Change #12

Section 10.1.2.3 Additional procedures for reporting serious adverse events

The following text has been removed:

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

Change #13

Table 10-1 Laboratory measurements

In the Biochemistry column for GGT footnote (b) was removed and footnote (a) was added.

Change #14

Table 10-2 Required investigations and follow up for PDILI

In the Evaluation column:

Monitoring of liver chemistry values at least twice per week for 2 weeks[c]

Immediate IMP discontinuation required if:

- Liver chemistry values continue to increase.

After 2 weeks of monitoring liver chemistry values:

- Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without stabilization or evidence of resolution

Continue to monitor until values normalize, stabilize, or return to within Baseline values[c]

Has been changed to:

Monitoring of liver chemistry values at least twice per week for 2 weeks[d]

Immediate IMP discontinuation required if:

- Liver chemistry values continue to increase.

After 2 weeks of monitoring liver chemistry values:

- Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without stabilization or evidence of resolution

Continue to monitor until values normalize, stabilize, or return to within Baseline values[d]

Change #15

Section 10.3 Other safety measurements

Other safety measurements include 12-lead ECGs, vital signs, physical examinations, neurological examination, psychiatric and mental status, body weight and height, and assessment of suicidality.

Has been changed to:

Other safety measurements include 12-lead ECGs, vital signs, physical examinations, neurological examination, body weight and height, and assessment of suicidality.

Change #16

Section 10.3.2 Vital signs

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

Has been changed to:

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).

Change #17

Section 10.3.5 Body weight and height

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram or pound) will be measured at time points specified in the schedule of study assessments.

Has been changed to:

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) will be measured at time points specified in the schedule of study assessments.

Change #18

Section 12.5 Handling of protocol deviations

Throughout the section, DRM was changed to DEM.

16.5 Appendix 5 - Protocol Amendment 2

Rationale

This purpose of this protocol amendment is to update the following:

- Update the number of subjects based on randomization of EP0083 and N01379 sites in Japan
- Update safety variables
- Update participating countries
- Include Independent Ethics Committee

In addition, minor administrative edits including typographical changes for formatting have been made.

Modifications and changes

Global changes

The Independent Ethics Committee (IEC) was added where IRB was mentioned throughout the document.

Specific changes

Change #1

Protocol Title

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

Has been changed to:

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

Change #2

IEC was added to the list of abbreviations

Change #3

Section 1 Summary

EP0085 is an open-label, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam (BRV) used as adjunctive treatment in Japanese subjects ≥16 years with partial seizures with or without secondary generalization. The primary objective is to evaluate the long-term safety and tolerability of BRV in focal epilepsy subjects with partial seizures. The secondary objective is to evaluate the maintenance of efficacy of BRV over time.

The subject population will be Japanese subjects with partial seizures with or without secondary generalization.

The primary safety variables include adverse events (AEs), withdrawals due to AEs, and occurrence of serious adverse events (SAEs). Other safety variables include safety laboratory tests (blood chemistry, hematology, and urinalysis), vital signs, body weight, electrocardiograms (ECGs), and physical and neurological examinations.

Have been changed to:

EP0085 is an open-label, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam (BRV) used as adjunctive treatment in subjects ≥16 years with partial seizures with or without secondary generalization. The primary objective is to evaluate the long-term safety and tolerability of BRV in focal epilepsy subjects with partial seizures. The secondary objective is to evaluate the maintenance of efficacy of BRV over time.

The subject population will be subjects with partial seizures with or without secondary generalization.

The primary safety variable is adverse events (AEs). **Exploratory** safety variables include safety laboratory tests (blood chemistry, hematology, and urinalysis), vital signs, body weight, electrocardiograms (ECGs), physical and neurological examinations, **and mental and psychiatric status.**

Change #4

Section 1 Summary

It is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of randomized subjects will complete EP0083 or enroll from N01379 sites in Japan.

Has been changed to:

Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan. It is estimated that approximately 124 Japanese subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enroll from N01379 sites in Japan.

Change #5

Section 2.5 Rationale for the study

EP0085 will explore the long-term safety and efficacy of BRV in Japanese subjects. EP0085 will include Japanese subjects who have completed EP0083 and will also provide the opportunity for Japanese subjects from N01379 continue BRV treatment. The proposed study is intended to provide evidence of the long-term safety and efficacy of BRV as adjunctive therapy in Japanese subjects with partial seizures. Doses of BRV 50 to 200mg/day will be assessed with reference to EP0083. EP0083 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in Asian subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. N01379 is an open-label, multicenter, long-term follow up study for N01358 which is the pivotal global efficacy study for BRV used as adjunctive treatment in adult subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization.

Has been changed to:

EP0085 will explore the long-term safety and efficacy of BRV in subjects. EP0085 will include subjects who have completed EP0083 and will also provide the opportunity for Japanese subjects from N01379 to continue BRV treatment. The proposed study is intended to provide evidence of the long-term safety and efficacy of BRV as adjunctive therapy in subjects with partial seizures. Doses of BRV 50 to 200mg/day will be assessed with reference to EP0083. EP0083 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. N01379 is an open-label, multicenter, long-term follow up study for N01358 which is the pivotal global efficacy study for BRV used as adjunctive treatment in adult subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization.

Change #6

Section 4 Study variables

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variables include:

- AEs
- Withdrawal due to AEs
- Occurrence of SAEs

4.1.2 Secondary safety variables

The secondary safety variables include:

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

Have been changed to:

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variable is AEs.

4.1.2 Exploratory safety variables

The exploratory safety variables are as follows:

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

- Body weight
- 12-lead ECG
- Physical examination
- Neurological examination
- **Mental status**
- **Psychiatric status**

Change #7

Section 5.1 Study description

The subject population will be Japanese subjects (≥16 years of age) with partial seizures with or without secondary generalization.

Subjects from N01379 can enter EP0085 at a dose up to 200mg/day. After Visit 1, the next visit for subjects entering from N01379 will be Visit 4 (Visit 2 and Visit 3 will not be conducted).

Have been changed to:

The subject population will be subjects (≥16 years of age) with partial seizures with or without secondary generalization.

Japanese subjects from N01379 can enter EP0085 at a dose up to 200mg/day. After Visit 1, the next visit for subjects entering from N01379 will be Visit 4 (Visit 2 and Visit 3 will not be conducted).

Change #8

Section 5.1.1 Study duration per subject

EP0085 will continue until the date of the market approval of BRV, or until the sponsor decides to close the study or until BRV development is stopped by the sponsor. EP0085 will continue as a postmarketing clinical study until approximately 6 months after the date of BRV approval for the partial seizure indication.

Have been changed to:

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

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

Change #9

Section 5.1.2 Planned number of subjects and sites

It is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of randomized subjects will complete EP0083 or enroll from N01379 sites in Japan.

It is estimated that 30 sites will participate in the study.

Has been changed to:

Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan.

It is estimated that approximately 124 **Japanese** subjects will enter the study, based on the assumption that at least 90% of randomized **Japanese** subjects will complete EP0083 or enroll from N01379 sites in Japan.

It is estimated that **65** sites will participate in the study.

Change #10

Section 5.1.3 Anticipated regions and countries

All sites in this study will be conducted in Japan.

Has been changed to:

The study is planned to be conducted in Japan, South Korea, Bulgaria, and Poland with possible extension to other countries or regions.

Change #11

Section 12 Statistics

The following sentence was added:

For subjects from EP0083, subgroup analyses for Japanese and non-Japanese subjects will be conducted as well as analyses for the entire population.

Change #12

Section 12.8 Determination of sample size

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

Has been changed to:

For this open-label LTFU study, no sample size calculation will be performed. The sample size will depend upon recruitment into and completion of the previous study. **Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan**. It is estimated that approximately 124 **Japanese** subjects will enter the study based on the assumption that at least 90% of randomized **Japanese** subjects will complete EP0083 or enter from N01379 sites in Japan.

16.6 Appendix 6 - Protocol Amendment 3

Rationale

The purpose of this protocol amendment is to update the following:

- Update the Sponsor/Local Legal Representatives
- Add China as a participating country
- Include SAE reporting information for China
- Update the number of subjects expected to enter the study
- Change exploratory safety variable to other safety variable

In addition, minor administrative edits including typographical changes for formatting have been made.

Modifications and changes

Global Changes

The "exploratory safety variable" language was changed to "other safety variable" throughout the protocol.

Specific changes

Change #1

STUDY CONTACT INFORMATION, Sponsor/Local Legal Representative

UCB Japan Co. Ltd.

Shinjuku Grand Tower

8-17-1 Nishi-Shinjuku

Shinjuku-ku

Tokyo 160-0023

JAPAN

Has been changed to:

UCB BIOPHARMA SPRL	UCB Japan Co. Ltd.	UCB Trading (Shanghai) Co., Ltd.
Allée de la Recherche 60	Shinjuku Grand Tower	317 Room No.[redacted]
	8-17-1 Nishi-Shinjuku	Futexi Yi road, China (Shanghai)
	Shinjuku-ku	Pilot Free Trade Zone
1070 Brussels	Tokyo 160-0023	Shanghai 200131
BELGIUM	JAPAN	PRC

Change #2

STUDY CONTACT INFORMATION

Medical Expert

Has been changed to:

Medical Expert **in Japan**

Change #3

STUDY CONTACT INFORMATION

A placeholder was added for the National Principal Investigator in China

Change #4

STUDY CONTACT INFORMATION, Sponsor Study Physician

Address:	Suite [redacted] Raffles City, Shanghai Office Tower, 268 Tibet Road Central, Shanghai 200001 PRC

Has been changed to:

Address:	Suite [redacted] Raffles City, Shanghai Office Tower, 268 Tibet Road Central, Shanghai 200001 PRC

Change #5

STUDY CONTACT INFORMATION, Clinical Project Manager

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

Has been changed to:

Name:	[redacted]
Address:	Allée de la Recherche 60 B- 1070 Brussels, BELGIUM
Phone:	[redacted]
Fax:	

Change #6

The following serious adverse event reporting information was added for China

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

Change #7

Summary, third paragraph, last sentence

The following sentence was removed.

In the event that subjects are converted to commercial BRV, they may complete the study without down-titration if, when, and where available.

Change #8

Summary, sixth paragraph, second sentence

Exploratory safety variables include safety laboratory tests (blood chemistry, hematology, and urinalysis), vital signs, body weight, electrocardiograms (ECGs), physical and neurological examinations, and mental and psychiatric status.

Has been changed to:

Other safety variables include safety laboratory tests (blood chemistry, hematology, and urinalysis), vital signs, body weight, electrocardiograms (ECGs), physical and neurological examinations, and mental and psychiatric status.

Change #9

Summary, last two paragraphs

Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan.

It is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of Japanese randomized subjects will complete EP0083 or enroll

Has been changed to:

~~Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan.~~

In Japan, it is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of Japanese randomized subjects will complete EP0083 or enroll from N01379 sites in Japan. **Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083.**

Change #10

Section 2.4 Safety with BRV

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

Has been changed to:

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

Change #11

Section 2.5 Rationale for the study

EP0085 will explore the long-term safety and efficacy of BRV in subjects. EP0085 will include subjects who have completed EP0083 and will also provide the opportunity for Japanese subjects from N01379 to continue BRV treatment.

Has been changed to:

EP0085 will explore the long-term safety and efficacy of BRV in subjects in **Japan and China**. EP0085 will include subjects who have completed EP0083. **In addition, the study** will also provide the opportunity for Japanese subjects from N01379 to continue BRV treatment.

Change #12

Section 4.1.2 Exploratory safety variables

The exploratory safety variables are as follows:

Has been changed to:

Section 4.1.2 Other safety variables

The other safety variables are as follows:

Change #13

Section 5.1 Study description, first sentence

EP0085 is a Phase 3, open-label, LTFU, multicenter, noncomparative, and dose flexible study.

Has been changed to:

EP0085 is a Phase 3, open-label, LTFU, multicenter, noncomparative, and dose flexible study **to be conducted in Japan and China**.

Change #14

Section 5.1.1 Study duration per subject, last two paragraphs

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

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

Has been changed to:

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

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

Change #15

Section 5.1.2 Planned number of subjects and sites, second paragraph

Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan.

It is estimated that approximately 124 Japanese subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enroll from N01379 sites in Japan.

It is estimated that 65 sites will participate in the study.

Has been changed to:

~~Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan.~~

In Japan, it is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enroll from N01379 sites in Japan. **Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083.**

In China Mainland, it is estimated that approximately 90 subjects will enter the study, based on the assumption that at least 90% of randomized Chinese subjects will complete EP0083.

It is estimated that **approximately 50 Japan sites and 25 China Mainland sites** will participate in the study.

Change #16

Section 5.1.3 Anticipated regions and countries

The study is planned to be conducted in Japan, South Korea, Bulgaria, and Poland with possible extension to other countries or regions.

Has been changed to:

The study is planned to be conducted in Japan and **China Mainland.**

Change #17

Section 7.2 Treatments to be administered, second paragraph

Subjects who entered from N01379 can enter EP0085 at a dose up to 200mg/day.

Has been changed to:

Subjects **from Japan** who entered from N01379 can enter EP0085 at a dose up to 200mg/day.

Change #18

Section 7.10 Randomization and numbering of subjects, last sentence in first paragraph

Subjects from N01379 can enter EP0085 at a dose up to 200mg/day.

Has been changed to:

Subjects from **Japan who participated in** N01379 can enter EP0085 at a dose up to 200mg/day.

Change #19

Section 12 Statistics, second sentence

For subjects from EP0083, subgroup analyses for Japanese and non-Japanese subjects will be conducted as well as analyses for the entire population.

Has been changed to:

For subjects from EP0083, subgroup analyses for Japanese **and Chinese** subjects will be conducted as well as analyses for the entire population.

Change #20

Section 12.8 Determination of sample size, second sentence

For this open-label LTFU study, no sample size calculation will be performed. The sample size will depend upon recruitment into and completion of the previous study. Approximately 227 subjects in total are expected to enter the study based on the assumption that 90% of randomized subjects will complete EP0083 in all participating countries or enroll from N01379 sites in Japan. It is estimated that approximately 124 Japanese subjects will enter the study based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enter from N01379 sites in Japan.

Has been changed to:

For this open-label LTFU study, no sample size calculation will be performed. The sample size will depend upon recruitment into and completion of the previous study. **In Japan**, it is estimated that approximately 124 Japanese subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enroll from N01379 sites in Japan. **Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083.**

16.7 Appendix 7 – Protocol Amendment 3.1 (Japan)

Rationale

The purpose of this local protocol amendment is to update the following:

- Add a cohort of directly enrolled subjects for sites in Japan.
- Add inclusion criteria for direct enrollers to avoid overlap with the patient population of EP0083.
- Remove LEV from the list of prohibited concomitant medications for directly enrolled subjects in Japan.

In addition, minor administrative edits including typographical changes for formatting have been made.

Global Changes

In Japan, a cohort of direct enrollers was added.

Modifications and changes

Specific changes

Change #1

Study contact information

The National Leading Principal Investigator in China information was removed for this local protocol amendment for Japan.

A fax number was added for the Clinical Project Manager

Change #2

Summary, third and fourth paragraphs

In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter into this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment. Subjects from N01379 can enter EP0085 at a dose up to 200mg/day.

Have been changed to:

Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter into this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

In addition, for accumulating safety data, subjects in Japan that have well-characterized focal epilepsy with seizures that are uncontrolled in spite of treatment with at least 1 permitted AED, having experienced 1 to <8 partial seizures within the 8 weeks prior to BRV administration may be directly enrolled.

Directly enrolled subjects and subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment. Subjects from N01379 can enter EP0085 at a dose up to 200mg/day.

Change #3

Summary, bulleted list of efficacy variables

The following efficacy variables for directly enrolled subjects in Japan were added:

- **Percent reduction in partial seizure frequency per 28 days from 8 weeks prior to BRV administration to the Evaluation Period**
- **Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure frequency from 8 weeks prior to BRV administration**
- **Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized, and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period**
- **Seizure freedom (partial, all epileptic seizure) during the Evaluation Period**

Change #4

Summary, last paragraph

In Japan, it is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enroll from N01379 sites in Japan. Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083.

Has been changed to:

Overall, approximately 217 subjects are planned for enrollment. In Japan, it is estimated that approximately **127** subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 **(approximately 90 subjects)** or enroll from N01379 sites in Japan **(7 subjects) and the plan that approximately 30 Japanese subjects will be directly enrolled in this study.** Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083 **(approximately 90 subjects).**

Change #5

Section 2.5, Rationale for the study

EP0085 will explore the long-term safety and efficacy of BRV in subjects in Japan and China. EP0085 will include subjects who have completed EP0083. In addition, the study will also provide the opportunity for Japanese subjects from N01379 to continue BRV treatment.

The proposed study is intended to provide evidence of the long-term safety and efficacy of BRV as adjunctive therapy in subjects with partial seizures. Doses of BRV 50 to 200mg/day will be assessed with reference to EP0083. EP0083 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. N01379 is an open-label, multicenter, long-term follow up study for N01358 which is the pivotal global efficacy study for BRV used as adjunctive treatment in adult subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization.

Has been changed to:

EP0085 will explore the long-term safety and efficacy of BRV in subjects in Japan and China. EP0085 will include subjects who have completed EP0083**,** Japanese subjects from N01379**, and directly enrolled Japanese subjects.**

The proposed study is intended to provide evidence of the long-term safety and efficacy of BRV as adjunctive therapy in subjects with partial seizures. Doses of BRV 50 to 200mg/day will be assessed with reference to EP0083. EP0083 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization. N01379 is an open-label, multicenter, long-term follow up study for N01358 which is the pivotal global efficacy study for BRV used as adjunctive treatment in adult subjects (≥16 to 80 years of age) with partial seizures with or without secondary generalization**. For sites in Japan, subjects with uncontrolled seizures treated by at least 1 permitted concomitant AED may be directly enrolled in order to provide additional safety and efficacy data with BRV.**

Change #6

Section 4.1.3, Efficacy variables

The following efficacy variables for directly enrolled subjects in Japan were added:

- **Percent reduction in partial seizure frequency per 28 days from 8 weeks prior to BRV administration to the Evaluation Period**
- **Responder rate in partial seizure frequency per 28 days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure frequency from 8 weeks prior to BRV administration**
- **Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized, and unclassified epileptic seizure) for at least 6 months and at least 12 months during the Evaluation Period**
- **Seizure freedom (partial, all epileptic seizure) during the Evaluation Period**

Change #7

Section 5.1, Study description, first 3 paragraphs

EP0085 is a Phase 3, open-label, LTFU, multicenter, noncomparative, and dose flexible study to be conducted in Japan and China. The subject population will be subjects (≥16 years of age) with partial seizures with or without secondary generalization. Subjects of a minor age are included

only where legally permitted and ethically accepted. Subjects must complete the Treatment and Transition Period of EP0083 prior to enrollment into EP0085.

In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, can enter into this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment.

Have been changed to:

EP0085 is a Phase 3, open-label, LTFU, multicenter, noncomparative, and dose flexible study to be conducted in Japan and China. The population will be subjects (≥16 years of age) with partial seizures with or without secondary generalization. Subjects of a minor age are included only where legally permitted and ethically accepted. **In Japan, subjects meeting the inclusion and exclusion criteria as specified in Section 6.1 may be directly enrolled. Rollover** subjects must complete the Treatment and Transition Period of EP0083 prior to enrollment into EP0085.

In addition, Japanese subjects participating in N01379, the long-term open-label extension to the Phase 3, placebo-controlled study N01358, **may enter** this study. Upon completion or early discontinuation from EP0085, there will be a Down-Titration Period, followed by a 2-week Study Drug-Free Period during which the subject will not receive study drug.

Directly enrolled subjects in Japan and rollover subjects from EP0083 will be started on oral BRV at a dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is unable to tolerate treatment.

Change #8

Section 5.1.1, Study duration per subject

Text added to define the Screening Visit for direct enrollers in Japan:

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

Change #9

Section 5.1.2, Planned number of subjects and sites, first paragraph

In Japan, it is estimated that approximately 124 subjects will enter the study, based on the assumption that at least 90% of randomized Japanese subjects will complete EP0083 or enroll from N01379 sites in Japan. Likewise, at least 90% of randomized Chinese subjects will be assumed to complete EP0083.

Has been changed to:

Overall, approximately 217 subjects are planned for enrollment. In Japan, it is estimated that approximately 127 subjects will enter the study. **This estimate assumes** that at least 90% of randomized Japanese subjects will complete EP0083 **(approximately 90 subjects)** or enroll

from N01379 sites in Japan **(7 subjects) and the plan that 30 Japanese subjects will be directly enrolled in this study.**

Change #10

Section 5.2, Schedule of study assessments

The title of Table 5-1 has been changed to:

Schedule of study assessments **for subjects transitioning from EP0083 to N01379**

Table 5-2 has been added, presenting the schedule of study assessments for directly enrolled subjects in Japan.

Change #11

Section 5.3, Schematic diagram

Table 5-3, Full visit schedule, was revised to add the Screening Visit for directly enrolled subjects in Japan.

Change #12

Section 5.4, Rationale for study design and selection of dose, first paragraph

Subjects from EP0083 will be started on a BRV dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment. Subjects who entered from N01379 can enter EP0085 at a dose up to 200mg/day. The BRV 50 to 200mg/day is approved as the effective dose of BRV for adults in EU/US without titration. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered as a symmetrical morning and evening dose except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study medication in the last week of down-titration is given only in the morning.

Has been changed to:

Directly enrolled subjects and subjects from EP0083 will be started on a BRV dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment. Subjects who entered from N01379 can enter EP0085 at a dose up to 200mg/day. The BRV 50 to 200mg/day is approved as the effective dose of BRV for adults in EU/US without titration. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered **in equal** morning and evening dose**s** except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day. Study medication in the last week of down-titration is given only in the morning.

Change #13

Section 6, Selection and withdrawal of subjects

The inclusion and exclusion criteria were reorganized to present them separately for China and Japan. Criteria for the directly enrolled cohort was added.

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 signed and dated by the subject or by parent(s) or legally representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Male/female subject from 16 years of age or older. Subjects who are not legal adults may only be included where legally permitted and ethically accepted.
3. Subject completed the Treatment Period and Transition Period of EP0083 or is ongoing in N01379 sites in Japan.
4. Subject for whom the Investigator believes a reasonable benefit from the long-term administration of BRV may be expected.
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. Subject/legally representative considered as reliable and capable of adhering to the protocol (eg, able to understand and complete diaries and questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

Exclusion criteria

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

1. Subject has developed hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol during the course of the core study.
2. Severe medical, neurological or psychiatric disorders, or laboratory values which may have an impact on the safety of the subject.
3. Poor compliance with the visit schedule or medication intake in the previous BRV studies.
4. Planned participation in any other clinical study of another investigational drug or device during this study.
5. Pregnant or lactating woman.

6. Any medical condition which, in the Investigator's opinion, warrants exclusion.
7. 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 the Entry Visit (EV).
8. Subject has >2 x upper limit of normal (ULN) of any of the following at the EV: 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%.

Have been changed to:

Eligibility criteria in Japan

Inclusion criteria for all subjects

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

1. An IRB/IEC approved written informed consent signed and dated by the subject or by parent(s) or legally representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Male/female subject from 16 years of age or older. Subjects who are not legal adults may only be included where legally permitted and ethically accepted.
4. Subject for whom the Investigator believes a reasonable benefit from the long-term administration of BRV may be expected.
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. Subject/legally representative considered as reliable and capable of adhering to the protocol (eg, able to understand and complete diaries and questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

Additional inclusion criteria for rollover subjects

In addition to the inclusion criteria for all subjects in Japan (Section 6.1.1), the following criteria must also be met for rollover subjects in Japan:

3. Subject completed the Treatment Period and Transition Period of EP0083 or is ongoing in N01379 sites in Japan.

Additional inclusion criteria for directly enrolled subjects

In addition to the inclusion criteria for all subjects in Japan (Section 6.1.1), the following criteria must also be met for directly enrolled subjects in Japan:

7. **Subject has a body weight ≥40kg at the Screening Visit (SV).**
8. **Subject has well-characterized focal epilepsy/epileptic syndrome according to the 1989 ILAE classification.**
9. **Subject has had an electroencephalogram (EEG) reading compatible with the clinical diagnosis of focal epilepsy within the last 10 years. If there is no appropriate EEG available within the last 10 years, a Baseline EEG must be scheduled at the SV and the results received before the EV.**
10. **Subject has 1 to <8 partial seizures (according to the 1981 ILAE classification) during the 8 weeks prior to BRV administration.**
11. **Subject's seizures are uncontrolled while treated by at least 1 permitted concomitant AED. Vagal nerve stimulation (VNS) will be allowed and counted as a concomitant AED.**

Exclusion criteria for all subjects

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

1. Subject has developed hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol during the course of the core study.
2. Severe medical, neurological or psychiatric disorders, or laboratory values which may have an impact on the safety of the subject.
4. Planned participation in any other clinical study of another investigational drug or device during this study.
5. Pregnant or lactating woman.
6. Any medical condition which, in the Investigator's opinion, warrants exclusion.

Exclusion criteria for rollover subjects

In addition to the exclusion criteria for all subjects in Japan (Section 6.1.4), the following exclusion criteria also apply for rollover subjects in Japan:

3. Poor compliance with the visit schedule or medication intake in the previous BRV studies.
7. 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 C-SSRS at the Entry Visit (EV).

8. Subject has >2xULN of any of the following at the EV: ALT, AST, 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%).

Exclusion criteria for directly enrolled subjects

In addition to the exclusion criteria for all subjects in Japan (Section 6.1.4), the following exclusion criteria also apply for directly enrolled subjects in Japan:

9. 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).

10. 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 C-SSRS at the SV.

11. Subject has >2xULN of any of the following at the SV: ALT, AST, 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 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.

12. Subject previously enrolled in this study or any other prior study with BRV as a dosing arm.

13. Subject has experienced febrile seizures exclusively. The occurrence of febrile seizures in addition to other unprovoked seizures is not exclusionary.

14. Subject/legal representative is not able to read and understand the Informed Consent form (ICF), Assent form, or daily record card (DRC) instructions.

15. Subject has a history or presence of status epilepticus during the 30 days preceding the SV.

16. Subject has a history or presence of known psychogenic nonepileptic seizures.

17. Study participant has been treated with vigabatrin and has visual field defects.

18. **Subject is 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 the SV.**
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 per investigator assessment. Stable arteriovenous malformations, meningiomas, or other benign tumors may be acceptable.**
20. **Subject has any clinical conditions (eg, bone marrow suppression, severe renal impairment) which, per investigator discretion, impair reliable participation in the study or necessitate the use of medication not allowed by protocol.**
21. **Subject has the presence of a terminal illness.**
22. **Subject has the presence of a serious infection.**
23. **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 Investigator.**
24. **Subject has clinically significant ECG abnormalities according to the Investigator.**
25. **Subject has known alcohol or drug addiction or abuse within the last 2 years.**

Eligibility criteria in China

Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent signed and dated by the subject or by parent(s) or legally representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Male/female subject from 16 years of age or older. Subjects who are not legal adults may only be included where legally permitted and ethically accepted.
3. Subject completed the Treatment Period and Transition Period of EP0083.
4. Subject for whom the Investigator believes a reasonable benefit from the long-term administration of BRV may be expected.
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. Subject/legally representative considered as reliable and capable of adhering to the protocol (eg, able to understand and complete diaries and questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

Exclusion criteria

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

1. Subject has developed hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol during the course of the core study.
2. Severe medical, neurological or psychiatric disorders, or laboratory values which may have an impact on the safety of the subject.
3. Poor compliance with the visit schedule or medication intake in the previous BRV studies.
4. Planned participation in any other clinical study of another investigational drug or device during this study.
5. Pregnant or lactating woman.
6. Any medical condition which, in the Investigator's opinion, warrants exclusion.
7. 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 the EV.
8. Subject has >2 x upper limit of normal (ULN) of any of the following at the EV: 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%).

Change #14

Section 7.2, Treatments to be administered, paragraphs 1, 2, and 3

Subjects will be started on a BRV dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment.

Subjects from Japan who entered from N01379 can enter EP0085 at a dose up to 200mg/day. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered as a symmetrical morning and evening dose except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day.

The first intake of study medication should occur in the evening of the day of the EV. Subjects should take tablets according to instructions provided by the Investigator.

Has been changed to:

Directly enrolled subjects in Japan and subjects rolling over from EP0083 will be started on a BRV dose of 100mg/day (2 equally divided doses administered twice daily) at study entry and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment.

Subjects from Japan who entered from N01379 can enter EP0085 at a dose up to 200mg/day. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability between 50mg/day and 200mg/day during the study and must always be administered **in equal** morning and evening dose**s** except the last week of down-titration. Of note, decreasing the dose should not exceed 50mg/day.

For all subjects, the first intake of study medication should occur in the evening of the day of the EV. Subjects should take tablets according to instructions provided by the Investigator.

Change #15

Section 7.8.1, Permitted concomitant treatments, first paragraph

At the beginning of EP0085, the concomitant AEDs that were used in EP0083 and N01379 are permitted.

Has been changed to:

At the beginning of EP0085, the concomitant AEDs that were used in EP0083 and N01379 are permitted **for rollover subjects. Subjects directly enrolled into EP0085 in Japan will enter the study receiving at least 1 permitted concomitant AED.**

Change #16

Section 7.8.2, Prohibited concomitant treatments

Additional text was added to note that LEV is permitted for directly enrolled subjects in Japan only.

- LEV **(LEV is not prohibited for directly enrolled subjects in Japan)**

Change #17

Section 8.1, Screening Visit (for direct enrollers in Japan only)

New section added to describe the tasks and procedures to be performed during the Screening Visit for direct enrollers.

Change #18

Section 8.2, Entry Visit (for direct enrollers in Japan only)

New section added to describe the tasks and procedures to be performed during the Entry Visit for direct enrollers.

Change #19

Section 8.3, Entry Visit (rollovers from China and Japan only)

Section heading revised to clarify the information presented describing the Entry Visit is for rollover subjects only.

Change #20

Section 8.4, Minimal Evaluation Visits (all subjects)

Section heading revised to clarify the information presented describing the MEV is for all subjects.

Change #21

Section 8.5, Full Evaluation Visits (all subjects)

Section heading revised to clarify the information presented describing the FEV is for all subjects.

Change #22

Section 8.6, Yearly Evaluation Visits (all subjects)

Section heading revised to clarify the information presented describing the YEV is for all subjects.

Change #23

Section 8.7, End of Study Visit or Early Discontinuation Visit (all subjects)

Section heading revised to clarify the information presented describing the EOS or EDV is for all subjects.

Change #24

Section 8.8, Final Visit (all subjects)

Section heading revised to clarify the information presented describing the FV is for all subjects.

Change #25

Section 8.9, Unscheduled Visit (all subjects)

Section heading revised to clarify the information presented describing the UV is for all subjects.

Change #26

Section 10.2, Laboratory measurements, seventh paragraph

Laboratory safety assessments at the EV will be taken from the last visit of EP0083 or N01379 and do not need to be recorded on the eCRF. Laboratory safety assessments will be performed at time points specified in the schedule of study assessments (Table 5–1).

Has been changed to:

For rollover subjects in China and Japan, laboratory safety assessments at the EV will be taken from the last visit of EP0083 or N01379 and do not need to be recorded on the eCRF. Laboratory safety assessments will be performed at time points specified in the schedules of study assessments (Table 5–1 **and Table 5-2**).

Change #27

Section 10.3.1, ECG, first paragraph

A standard 12-lead ECG will be performed at protocol specified time points according to the Study schedule of assessments (Table 5–1). At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF. At the FV, a 12-lead ECG is mandatory, except if the FV follows an EDV where ECG results were normal. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

Has been changed to:

A standard 12-lead ECG will be performed at protocol specified time points according to the schedule**s** of study assessments (Table 5–1 **and Table 5-2**).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF **at the EV**. At the FV, a 12-lead ECG is mandatory **for all subjects,** except if the FV follows an EDV where ECG results were normal. The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

Change #28

Section 10.3.2, Vital signs, first paragraph

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). At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF.

Has been changed to:

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**s** of study assessments (Table 5–1 **and Table 5-2**).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF **at the EV**.

Change #29

Section 10.3.3, Physical examination

A standard physical examination will be performed at time points specified in the schedule of study assessments (Table 5–1). At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF. Clinically significant new or worsened abnormalities will have to be reported as AEs.

Has been changed to

A standard physical examination will be performed at time points specified in the schedule**s** of study assessments (Table 5–1 **and Table 5-2**).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF **at the EV**. Clinically significant new or worsened abnormalities will have to be reported as AEs.

Change #30

Section 10.3.4, Neurological examination

A standard neurological examination will be performed at time points specified in the schedule of study assessments (Table 5–1). At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF. Clinically significant new or worsened abnormalities will have to be reported as AEs.

Has been changed to:

A standard neurological examination will be performed at time points specified in the schedules of study assessments (Table 5–1 **and Table 5-2**).

For rollover subjects in China and Japan, data will be obtained from the last visit of the previous study and should not be recorded in the eCRF **at the EV**. Clinically significant new or worsened abnormalities will have to be reported as AEs.

Change #31

Section 10.3.5, Body weight and height

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) will be measured at time points specified in the schedule of study assessments (Table 5–1). Height will be obtained from Visit 1 in EP0085.

Has been changed to:

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) will be measured at time points specified in the schedules of study assessments (Table 5–1 **and Table 5-2**).

For rollover subjects in China and Japan, height will be obtained from Visit 1 in EP0085. **For direct enrollers in Japan, height will be obtained at the SV only.**

Change #32

Section 12, Statistics, third paragraph

Subjects from N01379 will be analyzed separately.

Has been changed to:

Subjects from N01379 **and direct enrollers from Japan** will be analyzed separately.

Change #33

Section 12.3, Planned efficacy analyses

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

The 28-day adjusted seizure frequency will be calculated by dividing the number of partial seizures by the number of days for which the DRC was completed and multiplying by 28.

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

Has been changed to:

Planned efficacy analyses for rollover subjects in China and Japan include:

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

Planned efficacy analyses for directly enrolled subjects in Japan include:

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

Planned efficacy analyses for all subjects (directly enrolled in Japan and rollovers in China and Japan) include:

- Seizure frequency per 28 days for partial seizures by 3-month periods over the Evaluation Period.
- Seizure frequency per 28 days for all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.

- Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.
- Percentages of subjects continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period.
- Proportion of seizure-free days for partial seizure and all seizure types by 3-month periods over the Evaluation Period.
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period.

Change #34

Section 12.8, Determination of sample size

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

Has been changed to:

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

Change #35

Section 16.3, Appendix 3- List of antiepileptic drugs

Text was added to clarify that LEV is permitted only for directly enrolled subjects in Japan.

- Levetiracetam *****

***Concomitant LEV is allowed only for direct enrollment participants. In that case, LEV is counted as 1 AED.**

16.8 Appendix 8 – Protocol Amendment 4

Rationale

The purpose of this protocol amendment is to update the following:

- Update the Study Contact Information
- Change the primary safety variable from AEs to TEAEs, in alignment with other studies across the BRV development program
- Delete mental status/psychiatric status from the list of other safety variables to be collected; abnormal findings upon physical or neurological examination will be recorded as AEs
- Change the planned duration of EP0085 to allow participants to continue in the study until market approval in countries where market approval will be requested and for 2 years in countries where market approval will not be requested or obtained
- Add details regarding EP0085 subjects' participation in EP0118 for clarification purposes
- Add to the study withdrawal criteria that a suicide attempt will necessitate a subject's withdrawal from the study. This will eliminate the risk of another suicide attempt or completed suicide during the study in cases where the participant's recent suicidal ideation was not accurately reflected by the C-SSRS.
- Add information regarding numbering of directly enrolled subjects entering the study
- Add a statement for TEAE and SAE disclosure on public registries per the current UCB protocol template
- Remove 2 efficacy analyses from the previous list of analyses planned for all subjects per SAP amendments implemented following EP0085 protocol approval
- Correct the handling of protocol deviations text as there was no pooling of stratification levels for statistical analysis and there were no statistical assumptions for the primary analysis for this study.

In addition, minor clarifications and administrative edits including typographical changes for formatting have been made.

Modifications and changes

Global changes

References to AEs was changed to TEAEs to clarify that treatment-emergent AEs were to be collected during the study.

Specific changes

Change #1

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted]

Address:	Suite [redacted] Raffles City, Shanghai Office Tower, 268 Tibet Road Central, Shanghai 200001 PRC
Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted]
Address:	Suite [redacted] Raffles City, Shanghai Office Tower, 268 Tibet Road Central, Shanghai 200001 PRC
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Allée de la Recherche 60 B- 1070 Brussels, BELGIUM
Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted]
Address:	Shinjuku Grand Tower, 8-17-1 Nishi-Shinjuku, Shinjuku-Ku, Tokyo, 160-0023, JAPAN
Phone:	[redacted]
Fax:	
Name:	
Address:	Suite [redacted] Raffles City, Shanghai Office Tower, 268 Tibet Road Central, Shanghai 200001 PRC
Phone:	[redacted]
Fax:	

Clinical Trial Biostatistician

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

Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted]
Address:	Suite [redacted] Raffles City, Shanghai Office Tower, 268 Tibet Road Central, Shanghai 200040 PRC
Phone:	[redacted]
Fax:	

Change #2, Section 4.1.1 Primary safety variables

The primary safety variable is AEs.

Has been changed to:

The primary safety variable is TEAEs.

Change #3, Section 4.1.2 Other safety variables

The other safety variables are as follows:

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

Has been changed to:

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

Change #4, Section 5.1.1 Study duration per subject

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

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

Has been changed to:

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

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

Change #4, Section 6.3 Withdrawal criteria

- 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.

Has been changed to:

- In the event of a suicide attempt, the subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

  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.

Change #5, Section 7.10 Randomization and numbering of subjects

Subjects will continue with the 5-digit subject numbers assigned by the IVRS/IWRS in the preceding studies.

Has been changed to:

Subjects from EP0083 and N01379 will continue with the 5-digit subject numbers assigned by the IVRS/IWRS in the preceding studies. Directly enrolled subjects will receive a 5-digit number assigned by the IVRS/IWRS at Screening that serves as the subject identifier throughout the study.

Change #6, Section 10.1.1.1 Adverse events

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 ICF), 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.

Has been changed to:

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 ICF), 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.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

Change #7, Section 12.3 Planned efficacy analyses

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

The 28-day adjusted seizure frequency will be calculated by dividing the number of partial seizures by the number of days for which the DRC was completed and multiplying by 28.

Planned efficacy analyses for rollover subjects in China and Japan include:

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

Planned efficacy analyses for directly enrolled subjects in Japan include:

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

Planned efficacy analyses for all subjects (directly enrolled in Japan and rollovers in China and Japan) include:

- Seizure frequency per 28 days for partial seizures by 3-month periods over the Evaluation Period.
- Seizure frequency per 28 days for all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.
- Percentage of subjects continuously seizure-free for partial seizure and all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.
- Percentages of subjects continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period.
- Proportion of seizure-free days for partial seizure and all seizure types by 3-month periods over the Evaluation Period.
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period.

Has been changed to:

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

The 28-day adjusted seizure frequency will be calculated by dividing the number of partial seizures by the number of days for which the DRC was completed and multiplying by 28.

Planned efficacy analyses for rollover subjects in China and Japan include:

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

Planned efficacy analyses for directly enrolled subjects in Japan include:

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

Planned efficacy analyses for all subjects (directly enrolled in Japan and rollovers in China and Japan) include:

- Seizure frequency per 28 days for partial seizures by 3-month periods over the Evaluation Period.
- Seizure frequency per 28 days for all seizure types (partial, generalized and unclassified epileptic seizure) by 3-month periods over the Evaluation Period.
- Percentages of subjects continuously seizure-free for partial seizure and all seizure types for at least 6 months and at least 12 months during the Evaluation Period.
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period.

Change #8, Section 12.5 Handling of protocol deviations

After all CRFs have been retrieved and entered and queries addressed, and prior to locking the clinical database a Data Evaluation Meeting (DEM) will be held. The purpose of this 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.

Has been changed to:

After all CRFs have been retrieved and entered and queries addressed, and prior to locking the clinical database a Data Evaluation Meeting (DEM) will be held. The purpose of this DEM will be to assess the quality of the data for subsequent database lock, identify protocol deviations, and finalize analysis populations.

17 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

18 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

Name: ep0085-protocol-amend-4

Version: 1.0

Document Number: CLIN-000215404

Title: EP0085 Protocol Amendment 4

Approved Date: 16 Mar 2023

Document Approvals	
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