

## PROTOCOL N01379 AMENDMENT 3

### AN OPEN-LABEL, MULTICENTER, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN SUBJECTS AGED 16 YEARS OR OLDER WITH EPILEPSY

### PHASE 3

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## LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
β-hCG	beta-human chorionic gonadotropin
BRV	brivaracetam
CDMS	clinical data management system
Cr Cl	creatinine clearance
CRF	Case Report Form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DRC	daily record card
DRM	data review meeting
DTP	Down-Titration Phone Call
ECG	electrocardiogram
EDV	Early Discontinuation Visit
EEG	electroencephalogram
EV	Entry Visit
FDA	Food and Drug Administration
FEV	Full Evaluation Visit
FV	Final Visit
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related Quality of Life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board

iv	intravenous
IVRS	interactive voice response system
LEV	levetiracetam
LTFU	long-term follow-up
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA <sup>®</sup>	Medical Dictionary for Regulatory Activities
MEV	Minimal Evaluation Visit
MRI	magnetic resonance imaging
NA	not applicable
PBO	placebo
PK	pharmacokinetics
POS	partial onset seizure
PRN	pro re nata (as needed)
PS	Patient Safety
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Inventory
RBC	red blood cells
SAE	serious adverse event
SDV	source data verification
SOP	Standard Operating Procedure
SV2	synaptic vesicle protein 2
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
UV	Unscheduled Visit
TSH	thyroid-stimulating hormone
V	Visit
WBC	white blood cells
YEV	Yearly Evaluation Visit

## 1 SUMMARY

This is a Phase 3, open-label, long-term follow-up (LTFU), multicenter, noncomparative, and single-arm study of brivaracetam (BRV). The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in epilepsy subjects. The secondary objective is to evaluate the maintenance of efficacy of BRV over time. Exploratory objectives are to assess the effects of BRV on subjects' Health-related Quality of Life (HRQoL), obtain information on the direct medical resource use, explore any change in socio-professional status, and assess the role of gene variants of SV2 in affecting response to BRV (as part of a DNA analysis at the program level).

This study will enroll subjects ( $\geq 16$  years) from N01358 with refractory partial onset seizures (POS) whether or not secondarily generalized and subjects ( $\geq 16$  years) from N01258 with localization-related or generalized epilepsy. Subjects under 18 years may only be included where legally permitted and ethically accepted. Subjects have to complete the Treatment Period of N01358 or the Evaluation Period of N01258 prior to enrollment into N01379. Subjects from N01358 will be started on a BRV dose of 150mg/day 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 N01258 will start at a dose of BRV 200mg/day and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study. During the Evaluation Period, subjects will be invited to visit the clinical site monthly in the first 3 months and every 3 months thereafter. The completion of the Evaluation Period or early discontinuation from N01379 is followed by a Down-Titration Period of up to 4 weeks and by a subsequent Posttreatment Period (between 2 and 4 weeks) during which the subject does not receive study drug, or subjects will be converted without down-titration to commercial BRV if, when, and where available. Alternatively, subjects may transition into another BRV study, or be initiated without down-titration into a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific legal and regulatory requirements.

This LTFU study will run throughout the duration of the clinical development period of BRV, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults ( $\geq 16$  years) with refractory POS, whether or not secondarily generalized; until the Sponsor decides to close the study; until subjects transition to another BRV study; until a managed access program, named patient program, compassionate use program, or similar type of access program is established as allowed per country-specific requirement in addition to legal and regulatory guidelines; or until BRV development is stopped by the Sponsor.

The primary efficacy variable is the POS (type I) seizure frequency standardized to a 28-day duration. Seizure types are coded according to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), 1981. The primary efficacy variable will be summarized by 3-month periods over the Evaluation Period.

Secondary efficacy variables include the seizure frequency per 28 days for all seizure types (I+II+III), the proportion of seizure-free days for all seizure types (I+II+III), the

proportion of continuously seizure-free subjects for all seizure types (I+II+III), and the responder rate in POS (type I). A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358. Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.

Other efficacy variables for subjects from N01258 with generalized epilepsy include the generalized (type II) seizure days, seizure days per 28 days for all seizure types (I+II+III), proportion of seizure-free days for all seizure types (I+II+III), and proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period. Some variables may not be assessed if the number of subjects with generalized epilepsy is insufficient.

Other efficacy and pharmacoeconomic variables include the Patient Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P) scores, medical resources use, and socio-professional data during the first 2 years of the Evaluation Period.

Safety variables include adverse events (AEs), laboratory tests (hematology, blood chemistry, urinalysis, endocrinology, and pregnancy test), electrocardiogram (ECG), vital signs, physical and neurological examinations, the Hospital Anxiety and Depression Scale (HADS) scores, and body weight.

It is estimated that approximately 650 to 720 subjects from N01358 will enter the study, based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. Up to 100 subjects from N01258 may also be eligible. It is estimated that approximately 120 sites from N01358 and up to 25 sites from N01258 will participate in the study.

## 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 of epilepsy remains difficult, and there is an ongoing medical need for new antiepileptic drugs (AEDs). For a considerable proportion of patients, seizure freedom can still not be reached with the 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 is 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.

The classification of epileptic syndromes and seizure types is - and always was - a matter of ongoing debate. First published in 1960 and last updated officially in 1981 for seizures and 1989 for epilepsies (Commission on Classification and Terminology of the ILAE, 1981 and 1989), these ILAE classifications were based on concepts that, for the most part, predate modern technologies and concepts (Engel, 2006; ILAE [<http://www.ilae-epilepsy.org>]). The availability of these modern techniques, like long-term video electroencephalograms (EEG) and high-resolution magnetic resonance imaging (MRI), providing much more precise knowledge in regard to seizure type classifications and epileptic syndromes, led some epilepsy groups and scientists towards introducing competing classification systems (like the Cleveland Clinic Epilepsy Classification) and even debating how useful the currently used ILAE classification system is at all (Lüders et al, 2006).

This ongoing debate regarding the classification systems for epilepsies and seizures is also reflected within the latest Report of the Commission on Classification and Terminology (Classification Task Force) which proposes a thoroughly revised terminology and concept for the diagnosis of epilepsy syndromes and also to some extent seizure types (Berg et al, 2010).

Despite this ongoing debate, for the purpose of this study the seizure type classification will follow the 1981 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 (Commission on Classification and Terminology of the ILAE, 1981).

Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAE publication (Commission on Classification and Terminology of the ILAE, 1989).

## 2.2 Background information regarding product

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



Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of BRV absorption is not affected by food. The pharmacokinetics (PK) is dose-proportional (at least from 10mg to 600mg). Brivaracetam is weakly bound to plasma proteins ( $\leq 20\%$ ). 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  $\omega 1$ -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 subjects 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 ethinylestradiol 30 $\mu$ g and levonorgestrel 150 $\mu$ g. 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 studies. 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 (3.0 $\mu$ g/mL) at BRV doses of 100 and 150mg/day.

There is increasing research to assess the role of genetic variation on response to medicines, including antiepileptics (Goldstein et al, 2007). Preliminary research with BRV has suggested a possible role for variants in synaptic vesicle protein (SV2) genes in modulating response to the medicine. To explore this observation further and to broaden the pharmacogenetic information available for BRV, deoxyribonucleic acid (DNA) sampling is included in the study for subjects coming from N01358.

### **2.3 Efficacy of BRV in fixed-dose Phase 2/3 studies in POS**

Following completion of the Phase 2 studies (N01114 and N01193), clinical results supported further development of BRV for the adjunctive treatment of POS. Two adequate and well-controlled fixed-dose studies (N01252 and N01253) were conducted to assess BRV across a dose range of 5 to 100mg/day.

N01253 assessed BRV doses of 5, 20, and 50mg/day and provided statistically significant and clinically relevant evidence of the efficacy of BRV 50mg/day. N01252 assessed BRV doses of 20, 50, and 100mg/day. Although N01252 was not positive, it provided supporting evidence for the efficacy of BRV 100mg/day in subjects with epilepsy.

## **2.4 Safety of BRV**

In Phase 2/3 studies, a favorable safety and tolerability profile has been demonstrated for BRV. The discontinuation rate and the discontinuation rate due to treatment-emergent adverse events (TEAEs) were low for all studies. The most frequently reported TEAEs were headache, somnolence, dizziness, and fatigue. The overall incidence of serious adverse events (SAEs) was low. There were no clinically relevant changes in laboratory values, vital signs, or ECG abnormalities.

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

## **2.5 Study rationale**

UCB is developing BRV as an adjunctive antiepileptic treatment in subjects 16 years and older suffering from epilepsy. N01379 will give subjects who have completed N01358 or N01258 the opportunity to access BRV under the present protocol. N01358 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized. N01258 is a multicenter, 4-arm, randomized, parallel-group study evaluating the safety and tolerability of adjunctive BRV treatment administered as intravenous (iv) infusion or iv bolus in subjects with localization-related or generalized epilepsy from 16 to 70 years old.

N01379 will explore the long-term safety and efficacy of BRV in subjects with epilepsy while providing access to BRV for subjects who may benefit from open-label treatment with BRV.

# **3 STUDY OBJECTIVES**

## **3.1 Primary objective**

The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in epilepsy subjects.

## **3.2 Secondary objective**

- To evaluate the maintenance of efficacy of BRV over time

## **3.3 Exploratory objectives**

- To explore the effects of BRV on subjects' HRQoL
- To explore direct medical resource use
- To explore any change in socio-professional status

- To assess the role of gene variants of SV2 in affecting response to BRV (as part of a DNA analysis at the program level)

## **4 STUDY VARIABLES**

### **4.1 Safety variables**

#### **4.1.1 Primary safety variables**

- Occurrence of a TEAE
- Withdrawal due to AE
- Occurrence of an SAE

#### **4.1.2 Other safety variables**

- Laboratory tests (blood chemistry, hematology, urinalysis, endocrinology)
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) and body weight
- ECG
- Physical and neurological examinations
- Change in HADS scores from the Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

### **4.2 Efficacy variables**

#### **4.2.1 Secondary efficacy variables**

For subjects with focal-onset epilepsy:

- POS (type I) frequency per 28 days during the Evaluation Period
- Percent reduction in POS (type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate in POS (type I) frequency over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period of the previous study.

No secondary efficacy variables are defined for subjects with generalized epilepsy.

#### **4.2.2 Other efficacy variables**

For subjects with focal-onset epilepsy:

- Percentage of subjects continuously seizure-free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period

For subjects with generalized epilepsy:

- Generalized (type II) seizure days per 28 days during the Evaluation Period
- Percent reduction in generalized (type II) seizure days per 28 days from Baseline of the previous study to the Evaluation Period



- Responder rate for generalized (type II) seizure days over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure days from the Baseline Period of the previous study.
- Percentage of subjects continuously seizure free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period

The following will be evaluated separately for subjects with focal-onset epilepsy and subjects with generalized epilepsy:

- Change in QOLIE-31-P scores from Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

### 4.3 Pharmacoeconomic variables

The following will be evaluated separately for subjects with focal-onset epilepsy and subjects with generalized epilepsy:

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and emergency room visits) during the first 2 years of the Evaluation Period
- Socio-professional data for each assessment for the first 2 years and for the last assessment during the first 2 years of the Evaluation Period

## 5 STUDY DESIGN

### 5.1 Study description

This is a Phase 3, open-label, LTFU, multicenter, noncomparative, and single-arm study. The subject population will be adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized from N01358 and subjects with localization-related or generalized epilepsy from N01258. Subjects under 18 years may be included only where legally permitted and ethically accepted. Subjects must complete the Treatment Period of N01358 or the Evaluation Period of N01258 prior to enrollment into N01379. Upon completion of the Evaluation Period or early discontinuation from N01379 there will be a Down-Titration Period followed by a Posttreatment Period during which the subject does not receive study drug, or subjects will be converted without down-titration to commercial BRV if, when, and where available. Alternatively, subjects may transition into another BRV study, or be initiated without down-titration into a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific legal and regulatory requirements.

Subjects from N01358 will be started on oral BRV at a dose of 150mg/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 N01258 will be started at an oral dose of BRV 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study and must always be administered as a symmetrical morning and evening dose.

### 5.1.1 Study duration per subject

Subject recruitment for the study will begin in approximately Q2 2011. For each subject, the study will last from study entry until either regulatory approval of BRV has been granted by any Health Authority in an indication of adjunctive treatment of POS, until the Sponsor decides to close the study; until subjects transition to another BRV study; until a managed access program, named patient program, compassionate use program, or similar type of access program is established as allowed per country-specific requirement in addition to legal and regulatory guidelines; or until BRV development is stopped by the Sponsor.

The following study periods are defined:

- Evaluation Period (Visit 1 until the Last Evaluation Period Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in N01379 will immediately 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 20mg/day for 1 week should be included prior to the Posttreatment Period.
- Posttreatment Period (2 to 4 weeks): 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 Posttreatment Period for a minimum of 2 weeks and a maximum of 4 weeks, followed by a Final Visit (FV).
- The end of the study is defined as the date of the last visit of the last subject in the study.

For subjects who transition to another BRV study or a managed access program or similar type of program or who will be converted to commercial BRV if, when, and where available, the Down-Titration Period and FV are not applicable.

### 5.1.2 Planned number of subjects and sites

It is estimated that approximately 650 to 720 subjects from N01358 will enter the study, based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. Up to 100 subjects from N01258 may also be eligible for enrollment.

It is estimated that 120 sites from N01358 and up to 25 sites from N01258 will participate in the study.

### 5.1.3 Anticipated regions and countries

The regions and countries for enrollment will be the same as in the previous studies, N01358 and N01258. N01358 is planned to be performed in North America (Canada and USA), Western Europe, Latin America, Eastern Europe, Asia, and Africa, and N01258 is planned to be performed in the USA and Europe, with possible extension to other countries or regions for both studies.

**5.2 Schedule of study assessments****Table 5-1: Schedule of study assessments**

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV]) <sup>a</sup>	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	V1	V3, V5, V9...	V2, V4, V6, V8, V10...	V7...	NA	NA	NA	<b>5.3</b>
<b>Month</b>	M0	M2, M6, M18...	M1, M3, M9, M15, M21...	M12...	NA	NA	NA	<b>5.3</b>
<b>ASSESSMENTS</b>								
Written Informed Consent	X							13.1
Written Informed Consent for DNA analysis (for subjects from N01358)	X							13.1
Subject identification card dispensing	X							13.2
Verification inclusion/ exclusion criteria	X							6
Demographic data	X							8.1
Childbearing potential	X							8.1
General medical and procedures history	X <sup>b</sup>							8.1
Epilepsy history	X <sup>b</sup>							8.1
AED history	X <sup>b</sup>							8.1
Vital signs	X <sup>c</sup>	X	X	X	X		X	10.6.2

**Table 5-1: Schedule of study assessments**

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV])	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	<b>V1</b>	<b>V3, V5, V9...</b>	<b>V2, V4, V6, V8, V10...</b>	<b>V7...</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>5.3</b>
<b>Month</b>	<b>M0</b>	<b>M2, M6, M18...</b>	<b>M1, M3, M9, M15, M21...</b>	<b>M12...</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>5.3</b>
Weight and height <sup>d</sup>	X	X		X	X		X	10.6.3
Physical examination	X <sup>c</sup>	X		X	X		X	10.6.4
Neurological examination	X <sup>c</sup>	X		X	X		X	10.6.5
ECG <sup>e</sup>	X <sup>c</sup>	X		X	X		X	10.6.1
IVRS call	X	X	X	X	X		X	7.10
Daily record card dispensed	X	X	X	X	X			9
Daily record card retrieved		X	X	X	X		X	9
Recording of seizures	X <sup>b</sup>	X	X	X	X		X	9
QOLIE-31-P <sup>f</sup>		X		X	X			9.1.1
HADS <sup>f</sup>		X		X	X			10.6.7
Socio-professional data <sup>g</sup>				X	X			9.1.2
Hospital stays <sup>g</sup>	X <sup>c</sup>	X	X	X	X			9.1.5
Healthcare provider consultations not foreseen by protocol <sup>g</sup>	X <sup>c</sup>	X	X	X	X			9.1.4
Laboratory safety assessments <sup>h</sup>	X <sup>c</sup>	X	X <sup>i</sup>	X	X		X	10.5.1

**Table 5-1: Schedule of study assessments**

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV])	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	<b>V1</b>	<b>V3, V5, V9...</b>	<b>V2, V4, V6, V8, V10...</b>	<b>V7...</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>5.3</b>
<b>Month</b>	<b>M0</b>	<b>M2, M6, M18...</b>	<b>M1, M3, M9, M15, M21...</b>	<b>M12...</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>5.3</b>
Blood sampling for the DNA analysis <sup>l</sup>	X							10.5.2
Recording of AEs	X <sup>k</sup>	X	X	X	X	X	X	10.1
C-SSRS	X	X	X	X	X		X	10.6.6
Medical procedures	X	X	X	X	X		X	9.1.3
Concomitant AED	X <sup>l</sup>	X	X	X	X		X	7.8
Concomitant non-AED	X <sup>l</sup>	X	X	X	X		X	7.8
Drug dispensing	X	X	X	X	X			7
Drug return/accountability		X	X	X	X		X	7
End of study status <sup>m</sup>					X		X	8.8

AE=adverse event; AED=antiepileptic drug; CRF=Case Report Form; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid;

DTP=Down-Titration Phone Call; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit;

HADS=Hospital Anxiety and Depression Scale; IVRS=interactive voice response system; M=Month; MEV=Minimal Evaluation Visit; NA=not applicable;

QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory; V=Visit; YEV=Yearly Evaluation Visit

Note: Months and visit numbers are displayed for the first 2 years. The visit schedule described in Section 5.3 will be applied.

Note: At the EV, the IVRS call will be part of the N01358 or N01258 final visit.

<sup>a</sup> The Down-Titration Phone Call at the end of the Down-Titration Period is mandatory.

<sup>b</sup> General medical and procedures history, AED history, recording of seizures, and epilepsy history will be obtained from the Baseline of N01358 or N01258 and do not need to be recorded on the CRF for this study.

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

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV])	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	<b>V1</b>	<b>V3, V5, V9...</b>	<b>V2, V4, V6, V8, V10...</b>	<b>V7...</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>5.3</b>
<b>Month</b>	<b>M0</b>	<b>M2, M6, M18...</b>	<b>M1, M3, M9, M15, M21...</b>	<b>M12...</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>5.3</b>

<sup>c</sup> The following will be obtained from the last visit of N01358 or N01258 and do not need to be recorded on the CRF for this study: physical and neurological examination, vital signs, hospital stays, healthcare provider consultations not foreseen by the protocol, ECG, and laboratory assessments (hematology, blood chemistry, and urinalysis).

<sup>d</sup> Height will be obtained at Visit 1 in N01358 or N01258.

<sup>e</sup> At the FV, an ECG is mandatory, except if the FV follows an EDV where ECG results were normal.

<sup>f</sup> QOLIE-31-P and HADS are to be completed at the beginning of the visit by all subjects who are able to complete the assessments on their own. These will be collected only for the first 2 years.

<sup>g</sup> Socio-professional data, hospital stays, and healthcare provider consultations not foreseen by the protocol will be collected for all subjects for the first 2 years.

<sup>h</sup> Laboratory safety assessment includes hematology, blood chemistry, and urinalysis; where applicable (women with childbearing potential), a urine pregnancy test will be done. Endocrinology will be assessed at each YEV. In addition, liver function tests as described in Section 10.5.1 will be performed at the MEV in M3 and M9. Laboratory 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.

<sup>i</sup> Liver function tests are the only laboratory assessments done at the MEV in M3 and M9 (see Section 10.5.1).

<sup>j</sup> The DNA analysis is part of N01379 and will be performed only in adult subjects from N01358 after signing an additional Informed Consent form and where ethically accepted and authorized by regulatory agencies. Mentally impaired subjects will be excluded from the DNA analysis.

<sup>k</sup> Ongoing AEs at the time of subject completion of N01358 or N01258 will be obtained from the database for N01358 or N01258 and should not be recorded on the CRF for N01379 unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the CRF for N01379 with the onset date corresponding to the date of change in condition.

<sup>l</sup> Ongoing medications (AEDs and non-AEDs) at the time of subject completion of N01358 or N01258 will be obtained from the database for N01358 or N01258 and should not be recorded on the CRF for N01379 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the CRF for N01379 with the start date corresponding to the date of change in administration.

<sup>m</sup> 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



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

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV])	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	V1	V3, V5, V9...	V2, V4, V6, V8, V10...	V7...	NA	NA	NA	<b>5.3</b>
<b>Month</b>	M0	M2, M6, M18...	M1, M3, M9, M15, M21...	M12...	NA	NA	NA	<b>5.3</b>

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 may transition into another BRV study, or be initiated without down-titration in a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific legal and regulatory requirements, or for subjects who will be converted without down-titration to commercial BRV if, when, and where available.

### 5.3 Visit schedule

Visits to the clinical site will be scheduled as follows:

- First year:
  - First 3 months: 1 visit every month: Minimal Evaluation Visit (MEV) alternating with the Full Evaluation Visit (FEV)
  - Next 9 months: 1 visit every 3 months: FEV alternating with MEV
- Second and subsequent years:
  - 1 visit every 3 months: MEV alternating with FEV/Yearly Evaluation Visit (YEV)
  - The YEV will be performed every 12 months

A full visit schedule is presented in the following table.



**Table 5–2: Visit schedule**

<b>First year follow-up</b>		
<b>Month</b>	<b>Visit</b>	<b>Type of visit</b>
M0	V1	EV
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV <sup>b</sup>
M4	-	-
M5	-	-
M6	V5	FEV
M7	-	-
M8	-	-
M9	V6	MEV <sup>b</sup>
M10	-	-
M11	-	-
<b>Second year follow-up<sup>a</sup></b>		
<b>Month</b>	<b>Visit</b>	<b>Type of visit</b>
M12	V7	YEV
M15	V8	MEV
M18	V9	FEV
M21	V10	MEV

EV=Entry Visit; FEV=Full Evaluation Visit; M=month; MEV=Minimal Evaluation Visit; V=Visit;  
YEV=Yearly Evaluation Visit

Note: “-” denotes that no visit is scheduled in that month.

<sup>a</sup> Subsequent years will follow the same visit schedule.

<sup>b</sup> Liver function tests will be performed in addition to the assessments described in Section 8.3

## 5.4 Rationale for study design and selection of dose

In the previous study N01358, subjects will be randomized to an oral dose of BRV 100mg/day, BRV 200mg/day, or to matching PBO. In the previous study N01258, subjects will receive either a 60-second iv bolus or a 15-minute iv infusion at a dose of BRV 100mg twice daily (200mg/day). Previous Phase 2/3 clinical studies in POS and dose-response modeling suggest that optimal seizure frequency requires BRV doses of 50 to 100mg/day, with BRV 150mg/day possibly providing some additional benefit. Following consultation with regulatory authorities, it was recommended to also explore BRV 200mg/day to obtain data on the upper end of the dose response curve in N01358.

The starting doses in N01379 will be BRV 150mg/day for subjects from N01358 and BRV 200mg/day for subjects from N01258. The study entry doses will be taken as 2 equally divided oral doses administered twice daily. In Phase 2/3 studies for POS with BRV doses up to 150mg/day, the overall discontinuation rate and the discontinuation rate due to TEAEs was low and similar to PBO. The most frequently reported TEAEs at BRV doses up to 150mg/day were headache, somnolence, dizziness, and fatigue. 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 Inclusion criteria**

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

1. An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved written informed consent signed and dated by the subject or by parent(s) or legally acceptable representative. The consent form or a specific assent form, where required, will be signed and dated by minors. In countries and sites where a DNA analysis is accepted, an additional Informed Consent form will have to be signed by subjects coming from N01358. Deoxyribonucleic acid analysis will be performed only in adults, and the subject can withdraw consent to the use of the sample at any time. Mentally impaired subjects will be excluded. In case the consent is withdrawn, the site must request the destruction of the sample.
2. Male/female subject from 16 years or older. Subject under 18 years may only be included where legally permitted and ethically accepted.
3. Subject completed the Treatment Period of N01358 or the Evaluation Period of N01258.
4. Subject for whom the Investigator believes a reasonable benefit from the long-term administration of BRV may be expected.
5. Female subject without childbearing potential (premenarcheal, postmenopausal for at least 2 years, bilateral oophorectomy or tubal ligation, complete hysterectomy) are eligible. Female subject with childbearing potential are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake (or ethinylestradiol 50µg per intake if associated with any strong enzyme inducer [eg, carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, rifampicin]), monogamous relationship with vasectomized partner, or double-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 acceptable 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 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 investigational medicinal product (IMP) or comparative drugs as stated in this protocol during the course of the core studies
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

## 6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects who have signed an additional Informed Consent form for DNA analysis may withdraw their consent to the DNA analysis at any time and may continue their participation in the N01379 study.

Investigators should attempt to obtain information on subjects, in case of withdrawal or discontinuation.

For subjects considered as lost to follow-up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation.

The Investigator should make an effort, and document his/her effort, to complete the EDV and preferably also the FV.

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 Case Report Form (CRF) must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor whenever possible to discuss the withdrawal in advance.

When possible, the study medication will be progressively down-titrated in the case of discontinuation. During the Down-Titration Period, the dose may be decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 20mg/day for 1 week

will be included prior to the Posttreatment Period. The Down-Titration Period will be followed by a Posttreatment Period of a minimum of 2 weeks and a maximum of 4 weeks.

Stopping rules and discontinuation criteria for individual subjects may be, for example:

- Withdrawal for safety reasons by the Investigator: occurrence of status epilepticus, appearance of a more severe type of seizure, significant increase in liver enzymes, and any other significant safety reason, or if the subject develops an illness that would interfere with his/her continued participation.
- Subject and/or Investigator does not think that the investigational drug is effective (ie, lack or loss of efficacy).
- Lost to follow-up.
- Withdrawal of consent for personal reasons not related to AEs or lack/loss of efficacy.
- Other reason that has to be specified in the CRF.
- 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.
- Withdrawal criterion for subjects who completed a C-SSRS assessment at the Entry Visit:
  - Subject has active suicidal ideation as indicated by a positive response (“Yes”) to either Question 4 or 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.
- Withdrawal criteria for already enrolled subjects who did not complete a C-SSRS assessment at the Entry Visit:
  - Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the “Already Enrolled Subjects” version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
  - Subject had active suicidal ideation prior to study entry or since study start as indicated by a positive response (“Yes”) to either Question 4 or Question 5 of the “Already Enrolled Subjects” version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
  - Subject has active suicidal ideation as indicated by a positive response (“Yes”) to either Question 4 or 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.

After the decision of the subject’s discontinuation, the Investigator will provide the subject with information about available alternative treatments.

## **7 STUDY TREATMENTS**

### **7.1 Description of investigational medicinal product(s)**

■■■■■-coated tablets of BRV 10mg, BRV 25mg, and BRV 50mg will be used in this study. The tablets of BRV will be packaged in bottles.

The BRV 10mg dose (20mg/day) will be used only for down-titration.

### **7.2 Treatments to be administered**

Subjects from N01358 will be started on a BRV dose of 150mg/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 N01258 will be started at a BRV dose of 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment. The BRV dose can subsequently be adjusted based on the individual subject's seizure control and/or tolerability. However, the BRV dose should not exceed 200mg/day during the study.

The first intake of study medication should occur in the evening of the day of the Entry Visit (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 20mg/day for 1 week should be included prior to the Posttreatment Period.

### **7.3 Packaging**

Oral tablets of BRV 25mg and 50mg will be packaged in high density polyethylene bottles of 200 tablets, and the 10mg tablets will be packaged in bottles containing 38 tablets. Each container will have a unique, preprinted identification number.

The Investigator will inform each subject on how to take the drug and that an excess of drug is present in the bottle.

### **7.4 Labeling**

Clinical drug supplies will be labeled in accordance with the current International Conference on 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.

The label will be adapted to the size of the investigational product package.

### **7.5 Handling and storage requirements**

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

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

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (or designee) before further use of the IMP.

The Clinical Project Manager (or designee) will transmit the out-of-range temperature (copy of the temperature log, duration of the out-of-range temperature, if available) to the Clinical Supply Coordinator. Based on discussion with Quality Assurance, the Clinical Supply Coordinator will then provide the Clinical Project Manager (or designee) with instructions for the site regarding use of the IMP.

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 provided and kept up-to-date to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. The study medication disposition records, such as shipping, dispensing, and return records, and inventory logs, must be kept at the site, preferably in the pharmacy. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Drug Accountability form should include at least:

- Number of tablets dispensed to and returned by each subject, with the visit number, kit number, and subject's number
- Initials of the person who actually dispensed and/or received returned study medication
- Dates of the above
- Explanation of noncompliance

Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol

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

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

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

Periodically, and/or after completion of the study, all used (including empty boxes and bottles) and unused visit boxes and bottles must be reconciled and returned (preferably in their original package) to the Sponsor or its representative.



## 7.7 Procedures for monitoring subject compliance

The IMP (kits) will be supplied to the subjects at EV, FEV, MEV, YEV, Last Evaluation Period Visit, or EDV in case of early discontinuation.

The Investigator will instruct the subject to bring back at each visit, the kits with all original bottles (even empty) dispensed at the previous visit and containing all the remaining tablets of study medication.

Drug accountability must be done in the subject'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 document.

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

For any treatment other than the investigational product, including over-the-counter products, an accurate record must be kept in the clinic chart (source documentation) and in the CRF.

This record should include the name of the drug (preferably the brand name), the dose, the date(s) of administration, and the indication for use.

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

All concomitant AEDs except the ones specified in Section 7.8.2 are permitted during the study.

Benzodiazepines are allowed. If taken more than once a week, for any indication, a benzodiazepine will be considered as an AED. Each intake for PRN use must be listed individually in the CRF, either on the concomitant AED medication page or on the concomitant non-AED medication page, according to the indication.

Vagal nerve stimulation is allowed. Vagal nerve stimulation will be counted as a concomitant AED. Vagal nerve stimulation implantation must be recorded on the medical and procedures history CRF page.

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

The following concomitant AED medications are prohibited during the study:

- Felbamate (except if on stable dose during previous studies N01358 and N01258)
- Vigabatrin

## 7.9 Blinding

This is an open-label LTFU study of the preceding double-blind study N01358 and of the open-label randomized study N01258.

## **7.10 Randomization and numbering of subjects**

Since N01379 is an open-label LTFU study for N01358 and N01258, subjects will not be randomized to any treatment groups. Subjects from N01358 will start with a dose of BRV 150mg/day and will be maintained on that dose for at least 2 weeks, unless they are unable to tolerate the dose. Subjects from N01258 will start at a dose of BRV 200mg/day and should be maintained on that dose for at least 2 weeks, unless they are unable to tolerate the dose.

Subjects will continue with the 5-digit subject numbers assigned by the interactive voice response system (IVRS) in the preceding studies.

## **8 STUDY PROCEDURES BY VISIT**

Prior to any study activities, the subject or legal representative will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with regulatory requirements. Subjects from N01358 agreeing to the DNA analysis will have to sign an additional Informed Consent form. The subject or legal representative will be given adequate time to consider any information concerning the study, given to them by the Investigator or designee. As part of the informed consent procedure, the subject or legal representative will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study. Additionally, if applicable (according to the subject's age and local requirements), the subject will sign an IRB/IEC assent form.

### **8.1 Entry Visit**

- Written Informed Consent
- Additional written Informed Consent for subjects agreeing to DNA analysis
- Subject identification card dispensing
- Verification inclusion/exclusion criteria
- Demographic data
- Childbearing potential
- Weight
- IVRS call
- Daily record card (DRC) dispensed
- Medical procedures
- Blood sampling for the DNA analysis for consenting subjects coming from N01358. The DNA analysis will be performed in adult subjects where ethically accepted and authorized by regulatory agencies.
- Concomitant AED
- Concomitant non-AED



Ongoing medications (AEDs and non-AEDs) at the time of subject completion of N01358 or N01258 will be obtained from the database for N01358 or N01258 and should not be recorded on the CRF for N01379 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the CRF for N01379 with the start date corresponding to the date of change in administration.

- Recording of AEs

Ongoing AEs at the time of subject completion of N01358 or N01258 will be obtained from the database for N01358 or N01258 and should not be recorded on the CRF for N01379 unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the CRF for N01379 with the onset date corresponding to the date of change in condition.

- Drug dispensing
- Appointment for the next visit according to the schedule described in Section 5.3

The following data will be obtained from the Baseline of N01358 or N01258 and do not need to be recorded on the CRF for this study.

- General medical and procedures history
- AED history
- Recording of seizures
- Epilepsy history

The following data will be obtained from the last visit of N01358 or N01258 and do not need to be recorded on the CRF for this study.

- Vital signs
- Neurological examination
- Physical examination
- ECG
- Laboratory safety assessments: hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- Hospital stays
- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol

Height will be obtained from Visit 1 in N01358 or N01258.

## 8.2 Full Evaluation Visit

- QOLIE-31-P (for the first 2 years)
- HADS (for the first 2 years)
- Vital signs

- Weight
- Physical examination
- Neurological examination
- ECG
- IVRS call
- DRC dispensed
- DRC retrieved
- Recording of seizures
- Hospital stays (for the first 2 years)
- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol (for the first 2 years)
- Laboratory safety assessments: hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing
- Drug return/accountability
- Appointment for the next visit according to the schedule described in Section 5.3

### **8.3 Minimal Evaluation Visit**

- Vital signs
- IVRS call
- DRC dispensed
- DRC retrieved
- Recording of seizures
- Hospital stays (for the first 2 years)
- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol (for the first 2 years)
- Liver function tests will be performed in Month 3 (V4) and Month 9 (V6) as described in Section 10.5.1

- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing
- Drug return/accountability
- Appointment for the next visit according to the schedule described in Section 5.3

#### **8.4 Yearly Evaluation Visit**

- QOLIE-31-P (for the first 2 years)
- HADS (for the first 2 years)
- Vital signs
- Weight
- Physical examination
- Neurological examination
- ECG
- IVRS call
- DRC dispensed
- DRC retrieved
- Recording of seizures
- Hospital stays (for the first 2 years)
- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol (for the first 2 years)
- Socio-professional data (for the first 2 years)
- Laboratory safety assessments, including thyroid-stimulating hormone (TSH) assessments: hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing

- Drug return/accountability
- Appointment for the next visit according to the schedule described in Section 5.3

### 8.5 Unscheduled Visit

At any time, the subject may have an Unscheduled Visit (UV) if the Investigator or the subject and/or the legal representative consider it necessary. All information, including the reason for the UV, should be recorded in the appropriate sections of the CRF.

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

### 8.6 Last Evaluation Period Visit or Early Discontinuation Visit

For subjects who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available), the EDV will need to be completed; however, down-titration and FV are not applicable.

- QOLIE-31-P (if the EDV occurs within the first 2 years)
- HADS (if the EDV occurs within the first 2 years)
- Vital signs
- Weight
- Physical examination
- Neurological examination
- ECG
- IVRS call
- DRC dispensed (if applicable; DRC not dispensed if subject will not down-titrate)
- DRC retrieved
- Recording of seizures
- Hospital stays (if the EDV occurs within the first 2 years)

- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol (if the EDV occurs within the first 2 years)
- Socio-professional data (if the EDV occurs within the first 2 years)
- Laboratory safety assessments: hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing (if applicable; drug not dispensed if subject will not down-titrate)
- Drug return/accountability
- End of study status (if the subject will not down-titrate)

## **8.7 Down-Titration Phone Call**

- Recording of AEs

The Down-Titration Phone Call at the end of the Down-Titration Period is mandatory.

Down-titration is not applicable to subjects who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available).

## **8.8 Final Visit**

- Vital signs
- Weight
- Physical examination
- Neurological examination
- ECG (mandatory, except if the FV follows an EDV where ECG results were normal)
- IVRS call
- DRC retrieved
- Recording of seizures
- 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)
- Recording of AEs
- Suicidality assessment (C-SSRS)

- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug return/accountability
- End of study status

The FV is not applicable to subjects who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available).

## 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 and the number (where possible) of epileptic seizures will be recorded on the DRC, as well as the type of seizure (according to individual description of seizures), occurrence of clusters, intake of concomitant AEDs, undesirable events with start and end dates, healthcare provider consultations not foreseen per protocol, 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 CRF; 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 CRF.

The DRC will be considered as source documentation. The subject should be educated to complete the DRC on all days with seizures (eg, when taking evening tablets). Substantial noncompliance with diary completion (seizures recording) may result in subject discontinuation from the study at any time by the Investigator or the Sponsor.

### 9.1 Additional efficacy and pharmacoeconomic assessments

#### 9.1.1 QOLIE-31-P scores

The QOLIE-31-P - Version 2.0 (see Section 16.1) will be used to evaluate the HRQoL of study subjects (Cramer and Van Hammée, 2003).

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998) that includes 30 items grouped into 7 multi-item subscales: seizure worry (5 items), overall quality of life (2 items), emotional well-being (5 items), energy/fatigue (4 items), cognitive functioning (6 items), medication effects (3 items), social function (5 items), and a health status item. The subscale scores, the total score, and the health status item score are calculated according to the scoring algorithm defined by the author, with scores ranging from 0 to 100 and higher scores indicating better function. In addition to these 31 items, the

QOLIE-31-P contains 7 items assessing the degree of “distress” associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item). The QOLIE-31-P will be completed by subjects who are able to complete the assessments on their own, during the first 2 years at the FEV, YEV, Last Evaluation Period Visit, and EDV.

### **9.1.2 Socio-professional data**

Socio-professional data, such as highest level of education, current professional status, housing status, regular assistance, and ability to drive, will be collected at the YEV, Last Evaluation Period Visit, and EDV during the first 2 years.

### **9.1.3 Medical procedures**

Data on medical procedures (surgery, therapeutic and/or diagnostic, hospitalizations) undertaken during the study will be collected and recorded in the CRF. Electrocardiograms specific to this study will not be recorded on the medical procedures page of the CRF, but in the modules specifically designed for this purpose. Medical procedures will be recorded at the EV, FEV, MEV, YEV, Last Evaluation Period Visit, EDV, and FV during the entire study, but only the first 2 years of recording will be included in the outcome evaluation.

### **9.1.4 Healthcare provider consultations not foreseen by the protocol**

At the FEV, MEV, YEV, Last Evaluation Period Visit, and EDV, healthcare provider consultations not foreseen by the protocol will be recorded in the CRF. It will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation. At the EV, data will be obtained from the last visit of the previous study, N01358 or N01258, and do not need to be recorded on the CRF for this study. Healthcare provider consultations not foreseen by the protocol will be recorded for the first 2 years.

### **9.1.5 Hospital stays**

At the FEV, MEV, YEV, Last Evaluation Period Visit, and EDV, data on hospital stays will be collected in the CRF. It will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay. At the EV, data will be obtained from the last visit of the previous study, N01358 or N01258, and do not need to be recorded on the CRF for this study. Hospital stays will be recorded for the first 2 years.

## **10 ASSESSMENT OF SAFETY**

### **10.1 Adverse events**

#### **10.1.1 Definition of adverse event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which 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 signing the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the CRF even if no investigational product was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product 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.

#### **10.1.2 Procedures for reporting and recording adverse events**

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

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

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

#### **10.1.3 Description of adverse events**

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

Details for completion of the Adverse Event CRF (including judgment of relationship to study medication) are described in the CRF Completion Guidelines.

#### **10.1.4 Follow-up on adverse events**

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

If an AE is still ongoing at the end of the study for a subject, follow-up should be provided until resolution/stable level of sequelae, 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 their IMP.

#### **10.1.5 Rule for repetition of an adverse event**

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

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



### 10.1.6 Pregnancy

Should a subject become pregnant after the first intake of any IMP, UCB's Patient Safety (PS) department should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known and the following should be completed:

- The subject should return for an EDV.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the EDV.
- A Safety Follow-Up Visit should be scheduled 2 weeks after the subject has discontinued their IMP.

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

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, UCB will ask the Investigator or designee to contact the subject and his partner to request consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the subject's partner for completion.

Any 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. The health of the child may be followed for 12 months after birth for any significant medical issues.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form.

### 10.1.7 Overdose of investigational medicinal product

Excessive dosing (2 times of maximum dose beyond that is prescribed in the protocol and including overdose) should be recorded in the study drug dosing module of the CRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

### 10.1.8 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.

## 10.2 Serious adverse events

### 10.2.1 Definition of 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 one of the other outcomes listed in the definition of serious

(Important medical events may include 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 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 criterion. 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.)

### 10.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact details 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 provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

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

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 investigational product), 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 adverse events that the Investigator thinks may be associated with the investigational product must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

### **10.2.3 Follow-up of serious adverse events**

An SAE 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.

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

### **10.3 Immediate reporting of adverse events**

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product

### **10.4 Anticipated serious adverse events**

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure: convulsion. This original list will remain in effect for the duration of the protocol.

The list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 10.2.2.

### **10.5 Laboratory measurements**

#### **10.5.1 Safety laboratory assessments**

Laboratory assessments (including hematology, blood chemistry, endocrinology, and urinalysis) will be conducted using standard methods at a central laboratory. 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 11mL per sampling, which includes 3mL for hematology and 8mL for blood chemistry. In addition, a 10mL blood sample for the DNA analysis will be collected at the EV in consenting adult subjects from N01358.

The subject must be preferably fasting, but study medication intake must not be delayed.

The following laboratory assessments will be conducted:

Hematology	Blood chemistry	Urinalysis	Endo- crinology	Pregnancy
WBC	Glucose	Glucose	TSH <sup>a</sup>	β-hCG
RBC	Sodium	Ketones		
Hemoglobin	Potassium	Occult blood		
Hematocrit	Calcium	Protein		
MCV	Chloride	Nitrites		
MCH	Bicarbonate	Leukocytes		
MCHC	Phosphorus (inorganic)	Microscopic exam <sup>b</sup>		
Platelet count				
Lymphocytes (number, %)	Total protein			
Monocytes (number, %)	Albumin			
Neutrophils (number, %)	Total bilirubin <sup>c</sup>			
Eosinophils (number, %)	Alkaline phosphatase <sup>c</sup>			
Basophils (number, %)				
	AST (SGOT) <sup>c</sup>			
	ALT (SGPT) <sup>c</sup>			
	GGT <sup>c</sup>			
	Uric acid			
	Urea			
	Creatinine			

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); 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 Visit; RBC=red blood cells; TSH=thyroid-stimulating hormone; WBC=white blood cells; YEV=Yearly Evaluation Visit

<sup>a</sup> Thyroid-stimulating hormone will be assessed at each YEV.

<sup>b</sup> Including bacteria, cells, casts, and crystals will be performed for all samples.

<sup>c</sup> 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.

The creatinine clearance (Cr Cl) will be calculated by the Cockcroft's formula:

- Male:  $\text{Cr Cl mL/min} = [(140 - \text{age}) \times \text{body weight}] / [72 \times \text{serum creatinine (mg/dL)}]$
- Female:  $\text{Cr Cl mL/min} = [(140 - \text{age}) \times \text{body weight}] / [72 \times \text{serum creatinine (mg/dL)}] \times 0.85$

The result of the calculated creatinine clearance will be provided by the central laboratory. Urine pregnancy tests should be used at any time during the study if a pregnancy is suspected.

Laboratory safety assessments at the EV will be taken from the last visit of N01358 or N01258 and do not need to be recorded on the CRF. Thereafter, laboratory safety assessments will be performed at the FEV, YEV, Last Evaluation Period Visit, and EDV. In addition, liver function tests will be performed at MEVs (Visit 4 and Visit 6) during the first year. Endocrinology (TSH) measurements will be performed at YEVs only. Laboratory assessments will also be mandatory at the FV, except if the FV follows an EDV where laboratory results were normal.

Results for hematology, blood chemistry, urinalysis, endocrinology, and pregnancy tests will be provided by fax to the Investigator within 72 hours after sample receipt. Results will be reported by the central laboratory to the Investigator as exact values, with a flag to those values that are outside the therapeutic range.

### **10.5.2 DNA analysis**

For subjects coming from N01358, a blood sample for DNA analysis will be collected at the EV in order to explore a possible correlation between the SV2 gene variations and the subject's response to BRV. Blood samples for DNA analysis will be collected only in adults where ethically accepted and authorized by legal authorities. The DNA analysis will be done in a separate report at the program level.

Samples will be split into 2 aliquots and will be initially stored at the central laboratory and will then be shipped to the genotyping facility for DNA extraction and genotyping. Samples will be stored at -20°C for a period of up to 20 years.

## **10.6 Other safety measurements**

### **10.6.1 Electrocardiogram**

A standard 12-lead ECG will be performed at the FEV, YEV, Last Evaluation Period Visit, EDV, and the FV. At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the CRF. At the FV, an 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.

The original ECG tracing will be signed or initialed and dated by the Investigator and retained as part of the source data. Copies of all ECG tracings will be retrieved for all subjects presenting treatment-emergent clinically significant abnormalities during the study.

## **10.6.2 Vital signs**

At each visit, supine or sitting pulse rate and blood pressure after 5 minutes rest will be measured. At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the CRF.

## **10.6.3 Body weight and height**

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram or pound) will be measured at the EV, FEV, YEV, Last Evaluation Period Visit, EDV, and FV. Height will be obtained from Visit 1 in N01358 or N01258.

## **10.6.4 Physical examination**

A standard physical examination will be performed at the FEV, YEV, Last Evaluation Period Visit, EDV, and FV. At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the CRF. Clinically significant new or worsened abnormalities will have to be reported as AEs.

## **10.6.5 Neurological examination**

A standard neurological examination will be performed at the FEV, YEV, Last Evaluation Period Visit, EDV, and FV. At the EV, data will be obtained from the last visit of the previous study and should not be recorded in the CRF. Clinically significant new or worsened abnormalities will have to be reported as AEs.

## **10.6.6 Assessment of suicidality**

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures, Section 5.2.

## **10.6.7 HADS scores**

The HADS (see Section 16.2) will be used to evaluate anxiety and depression/depressed mood of study subjects (Zigmond and Snaith, 1983). The HADS is an instrument that assesses the presence and severity of anxiety and depressed mood. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension (anxiety, depression) is calculated as recommended by the authors, ranging from 0 to 21 with higher scores indicating higher depression/anxiety. The HADS will be completed by subjects who are able to complete the assessments on their own, during the first 2 years at the FEV, YEV, Last Evaluation Period Visit, and EDV.

# **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 of the sponsor within 24 hours and follow any local regulatory requirements. 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 appropriate regulatory authorities, if applicable, prior to being implemented.

The Investigator/institution should conduct the study in compliance with the protocol agreed to by the Sponsor and, if applicable, by the appropriate regulatory authority(ies) and which has been approved by the IRB/IEC. The Investigator/institution and the Sponsor should sign the protocol to confirm agreement.

In exceptional circumstances, subject-specific deviations from the protocol may occur. All deviations should be recorded on an ongoing basis to allow regular assessment for the need of an amendment. Protocol deviations could invalidate the insurance coverage.

Any protocol deviation will be documented and explained by the Investigator or the person designated by the Investigator and will be included in the final Clinical Study Report.

## **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 contract research organization (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 CRFs 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 CRFs, 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 of CRFs are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

If they are not included in the clinical dossier/hospital file of the subjects, the following data may be written directly in the CRF and will therefore be considered as source data:



- Healthcare provider consultations not foreseen by the protocol
- Socio-professional data

Original laboratory results and ECG reports will be inserted in the CRF and are also to be considered as source data. Original QOLIE-31-P and HADS questionnaires will be retrieved. The site will keep a copy in the CRF and this copy will be considered as source data.

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 authorize 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 EEG records must be saved and stored as instructed by UCB (or designee).

For subjects receiving investigational product(s), the minimum requirements for source documents used in clinical studies are that they should contain the identity of the subject and study-related identifiers (such as treatment number, CRF number, or similar), they should mention the subject's participation in the study and identification of that study (study title or number), they should record the obtaining of consent (date of consent), the exposure to investigational product, the subject's medical history, the concomitant medication treatments and dates (including contraceptive treatment), AEs and SAEs, and the dates of the visits. The source documents should provide evidence that inclusion/exclusion criteria have been met.

### **11.2.2 Source data verification**

Source data verification (SDV) 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 CRF should be supported by source documents, unless otherwise specified in Section 11.2.1.

Information recorded in the CRF must be consistent with entries in the source documents. The monitor will perform 100% SDV.

## **11.3 Data handling**

### **11.3.1 Case Report Form completion**

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports.

Any change or correction to the CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted.

Corrections made after the Investigator's review and signature of the completed CRF will be resigned and dated by the Investigator.

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

Detailed instructions will be provided in the CRF Completion Guidelines.

### **11.3.2 Database entry and reconciliation**

Case Report Forms/external electronic data will be entered/loaded in a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report Form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person.

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 investigational products and other material in accordance with UCB procedures for the study.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- Return of all study data to UCB or its representatives while maintaining original source documents.
- Data clarification and/or resolution.
- Accountability, reconciliation, and arrangements for used and unused investigational products.
- Review of site study records for completeness.
- Discussion/reminder on archiving responsibilities.
- Discussion of IRB/IEC requirements for study termination.

- Arrangements for unused CRFs, laboratory supplies, and any other study-related supplies.

## **11.5 Archiving and data retention**

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

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

## **11.6 Audit and inspection**

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

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH/GCP, and applicable regulatory requirements.

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

## **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 is presented below and will be described in more detail in the Statistical Analysis Plan.

### **12.1 Definition of analysis populations**

Efficacy Populations will consist of all subjects who took at least 1 dose of study medication and have at least 1 seizure diary day during the Evaluation Period. Separate Efficacy

Populations will be defined for subjects with focal epilepsy and subjects with generalized epilepsy.

The Safety Population will consist of all subjects who took at least 1 dose of study medication.

## **12.2 General statistical considerations**

Descriptive statistics, such as the mean, standard deviation, median, 25th percentile, 75<sup>th</sup> percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Summary statistics will be presented for all subjects combined.

## **12.3 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 for all subjects and by categories of total duration of exposure.

All safety variables will be analyzed by descriptive methods on the Safety Population. Treatment-emergent adverse events will be summarized in incidence tables by categories of total duration of exposure and by Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) 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, as well as physical and neurological abnormalities, will also be listed by period and visit.

## **12.4 Planned efficacy analyses**

All efficacy outcomes will be summarized with descriptive statistics only. Separate summaries will be provided for subjects with focal epilepsy and subjects with generalized epilepsy.

For subjects with focal epilepsy, 28-day adjusted seizure frequency will be calculated by dividing the number of partial seizures by the number of days for which the diary was completed, and multiplying the resulting value by 28. For subjects with generalized epilepsy, 28-day adjusted seizure days will be calculated by dividing the number of days with a generalized seizure by the number of days for which the diary was completed, and multiplying the resulting value by 28.

Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.

Some variables for subjects with generalized epilepsy may not be assessed if the number of subjects with generalized epilepsy is insufficient.

Change in QOLIE-31-P scores from Baseline of the previous study will be summarized with descriptive statistics for the first 2 years of the Evaluation Period.

## **12.5 Planned pharmacoeconomic analyses**

Direct cost parameters and socio-professional data will be summarized with descriptive statistics for the first 2 years of the Evaluation Period.

## **12.6 Handling of protocol deviations**

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

## **12.7 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 categories of duration of exposure.

## **12.8 Planned interim analysis and data monitoring**

Due to the single-arm open-label nature of this study, no interim analysis as such will be performed. However, interim database snapshots may be performed to allow safety and efficacy analyses in support of submission activities or to allow optimization of the development program. In addition, an ongoing medical review (Safety Data Review) applying to the entire BRV program is organized.

## **12.9 Determination of sample size**

For this open-label LTFU, no sample size calculation will be performed. The sample size will depend upon recruitment into and completion of the previous studies. It is estimated that approximately 650 to 720 subjects from N01358 will enter the study based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. Up to 100 subjects from N01258 may also be eligible.

# **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 written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). An additional written Informed Consent form should be signed and dated for adult subjects from N01358 (without



mental impairment) giving their consent to blood sampling for DNA analysis. The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

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

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

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

### **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 name of the study and medical emergency contact information. The Investigator will instruct the subject to keep the card with them 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, Informed Consent form(s), Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the

original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on the Committee's 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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Sander JW, Shorvon SD. Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatry*. 1996;61:433-43.

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

## 16.3 Protocol Amendment 1

### Rationale for the amendment

This protocol amendment is issued to include a DNA analysis in order to assess the role of gene variants of SV2 in affecting response to BRV. The DNA analysis applies to adult subjects from N01358 without mental impairment and where legally acceptable and authorized by regulatory agencies. All related sections were updated accordingly. Furthermore, subjects coming from N01258 will also have the option to enroll in N01379 in addition to subjects from N01358 and the respective sections were revised. The laboratory section and the impacted study visits were updated to include assessments of liver function at 3-monthly intervals during the first year and a yearly TSH measurement in response to a regulatory agency request. Administrative changes include the update of the Sponsor company name and of the contact details. A few changes of editorial nature are not listed in the specific changes section.

### Modifications and changes

#### Global changes

- The following changes were made throughout the protocol.
- Procedures related to the DNA analysis and respective blood samplings have been added to various sections.
- N01379 will now include subjects coming from N01358 and from N01258. A reference to N01258 has been added to various impacted sections. As a consequence of the inclusion of subjects from N01258, various paragraphs relating to the study entry dose, efficacy variables, and analysis of efficacy variables were updated.
- The laboratory section and the impacted study visits were updated as follows:
  - Liver function tests will be performed in 3-month intervals during the first year.
  - Thyroid-stimulating hormone will be assessed at all YEVs.

#### Specific changes

##### Change #1

#### TITLE PAGE, SPONSOR NAME

Original text

SCHWARZ BIOSCIENCES, INC.

A Member of the UCB Group of Companies

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

**Has been changed to:**

UCB BIOSCIENCES, INC.  
8010 Arco Corporate Drive  
Raleigh, NC 27617  
UNITED STATES

**Change #2**

**SPONSOR DECLARATION**

Original text

**Clinical Project Manager**

██████████ MPH, MBA

\_\_\_\_\_  
Date/Signature

**Clinical Trial Biostatistician**

██████████, MS

\_\_\_\_\_  
Date/Signature

**Study Physician**

Dr. ██████████, MD, MBA

\_\_\_\_\_  
Date/Signature

**Clinical Program Director**

██████████, MD, PhD

\_\_\_\_\_  
Date/Signature

**Has been changed to:**

**Clinical Project Manager**

██████████, MPH, MBA

\_\_\_\_\_  
Date/Signature

**Clinical Trial Biostatistician**

██████████, MS

\_\_\_\_\_  
Date/Signature

**Study Physician**

██████████, MD

\_\_\_\_\_  
Date/Signature

**Clinical Program Director**

██████████, MD, PhD

\_\_\_\_\_  
Date/Signature

**Change #3**

**STUDY CONTACT INFORMATION**

Original text

Sponsor

SCHWARZ BIOSCIENCES, INC.

A Member of the UCB Group of Companies

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

**Has been changed to:**

**Sponsor**

UCB BIOSCIENCES, INC.

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

**Change #4**

**STUDY CONTACT INFORMATION, Sponsor Study Physician**

Original text

Name:	Dr. ██████████, MD, MBA
Address:	Alfred-Nobel-Straße 10 40789 Monheim Germany
Phone:	██████████
Fax:	██████████

**Has been changed to:**

Name:	██████████, MD
-------	----------------

<b>Address:</b>	<b>8010 Arco Corporate Drive, Suite 100</b> Raleigh, NC 27617 United States	
Phone:		
Fax:		

## Change #5

### LIST OF ABBREVIATIONS

The following explanations have been added to the list of abbreviations:

<b>DNA</b>	<b>deoxyribonucleic acid</b>
<b>iv</b>	<b>Intravenous</b>
<b>SV2</b>	<b>synaptic vesicle protein 2</b>
<b>TSH</b>	<b>thyroid-stimulating hormone</b>

## Change #6

### Section 1 SUMMARY

#### Original text

This is a Phase 3, open-label, long-term follow-up (LTFU), multicenter, noncomparative, and single-arm study of brivaracetam (BRV). The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in focal epilepsy subjects. The secondary objective is to evaluate the maintenance of efficacy of BRV over time. Exploratory objectives are to assess the effects of BRV on subjects' Health-related Quality of Life (HRQoL), obtain information on the direct medical resource use, and explore any change in socio-professional status.

This study will enroll adults ( $\geq 16$  years) with refractory partial onset seizures (POS) whether or not secondarily generalized. Subjects under 18 years may only be included where legally permitted and ethically accepted. Subjects have to complete the Treatment Period of N01358 prior to enrollment into N01379. They will be started on a BRV dose of 150mg/day at study entry and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study. During the Evaluation Period, subjects will be invited to visit the clinical site monthly in the first 3 months and every 3 months thereafter. The completion of the Evaluation Period or early discontinuation from N01379 is followed by a Down-Titration Period of up to 4 weeks and by a subsequent Posttreatment Period (between 2 and 4 weeks) during which the subject does not receive study drug.

This LTFU study will run throughout the duration of the clinical development period of BRV, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults ( $\geq 16$  years) with refractory POS, whether or not secondarily generalized, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

The primary efficacy variable is the POS (type I) seizure frequency standardized to a 28-day duration. Seizure types are coded according to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), 1981. The primary efficacy variable will be summarized by 3-month periods over the Evaluation Period.

Secondary efficacy variables include the seizure frequency per 28 days for all seizure types (I+II+III), the proportion of seizure-free days for all seizure types (I+II+III), the proportion of continuously seizure-free subjects for all seizure types (I+II+III), and the responder rate in POS (type I). A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

Other efficacy variables include the Patient Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P) scores, the Hospital Anxiety and Depression Scale (HADS) scores, medical resources use, and socio-professional data during the first 2 years of the Evaluation Period.

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

It is estimated that approximately 650 to 720 subjects will enter the study, based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. It is estimated that approximately 120 sites will participate in the study.

#### **Has been changed to:**

This is a Phase 3, open-label, long-term follow-up (LTFU), multicenter, noncomparative, and single-arm study of brivaracetam (BRV). The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in epilepsy subjects. The secondary objective is to evaluate the maintenance of efficacy of BRV over time. Exploratory objectives are to assess the effects of BRV on subjects' Health-related Quality of Life (HRQoL), obtain information on the direct medical resource use, explore any change in socio-professional status, **and assess the role of gene variants of SV2 in affecting response to BRV (as part of a DNA analysis at the program level).**

This study will enroll **subjects ( $\geq 16$  years) from N01358** with refractory partial onset seizures (POS) whether or not secondarily generalized **and subjects ( $\geq 16$  years) from N01258 with localization-related or generalized epilepsy.** Subjects under 18 years may only be included where legally permitted and ethically accepted. Subjects have to complete the Treatment Period of N01358 **or the Evaluation Period of N01258** prior to enrollment into N01379. **Subjects from N01358** will be started on a BRV dose of 150mg/day 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 N01258 will start at a dose of BRV 200mg/day and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment.** The BRV dose can be adjusted based on the individual subject's seizure



control and tolerability. However, the BRV dose may not exceed 200mg/day during the study. During the Evaluation Period, subjects will be invited to visit the clinical site monthly in the first 3 months and every 3 months thereafter. The completion of the Evaluation Period or early discontinuation from N01379 is followed by a Down-Titration Period of up to 4 weeks and by a subsequent Posttreatment Period (between 2 and 4 weeks) during which the subject does not receive study drug.

This LTFU study will run throughout the duration of the clinical development period of BRV, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults ( $\geq 16$  years) with refractory POS, whether or not secondarily generalized, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

The primary efficacy variable is the POS (type I) seizure frequency standardized to a 28-day duration. Seizure types are coded according to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), 1981. The primary efficacy variable will be summarized by 3-month periods over the Evaluation Period.

Secondary efficacy variables include the seizure frequency per 28 days for all seizure types (I+II+III), the proportion of seizure-free days for all seizure types (I+II+III), the proportion of continuously seizure-free subjects for all seizure types (I+II+III), and the responder rate in POS (type I). A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358. **Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.**

**Other efficacy variables for subjects from N01258 with generalized epilepsy include the generalized (type II) seizure days, seizure days per 28 days for all seizure types (I+II+III), proportion of seizure-free days for all seizure types (I+II+III), and proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period. Some variables may not be assessed if the number of subjects with generalized epilepsy is insufficient.**

Other **nonseizure-related** efficacy variables include the Patient Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P) scores, the Hospital Anxiety and Depression Scale (HADS) scores, medical resources use, and socio-professional data during the first 2 years of the Evaluation Period.

Safety variables include adverse events (AEs), laboratory tests (hematology, blood chemistry, urinalysis, **endocrinology**, and pregnancy test), electrocardiogram (ECG), vital signs, physical and neurological examinations, and body weight.

It is estimated that approximately 650 to 720 subjects **from N01358** will enter the study, based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. **Up to 100 subjects from N01258 may also be eligible.** It is estimated that approximately 120 sites **from N01358 and up to 25 sites from N01258** will participate in the study.

#### **Change #7**

## Section 2.2 Background information regarding product

### The following paragraph has been added to the original text.

There is increasing research to assess the role of genetic variation on response to medicines, including antiepileptics (Goldstein et al, 2007). Preliminary research with BRV has suggested a possible role for variants in synaptic vesicle protein (SV2) genes in modulating response to the medicine. To explore this observation further and to broaden the pharmacogenetic information available for BRV, deoxyribonucleic acid (DNA) sampling is included in the study for subjects coming from N01358.

#### Change #8

### Section 2.5 Study rationale

#### Original text

UCB is developing BRV as an adjunctive antiepileptic treatment in subjects 16 years and older suffering from focal epilepsy. N01379 will give subjects who have completed N01358 the opportunity to access BRV under the present protocol. N01358 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized.

N01379 will explore the long-term safety and efficacy of BRV in subjects with POS whether or not secondarily generalized while providing access to BRV for subjects who may benefit from open-label treatment with BRV.

#### Has been changed to:

UCB is developing BRV as an adjunctive antiepileptic treatment in subjects 16 years and older suffering from epilepsy. N01379 will give subjects who have completed N01358 **or N01258** the opportunity to access BRV under the present protocol. N01358 is an adequate and well-controlled study to provide additional data confirming the efficacy and safety of BRV as an AED in adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized. **N01258 is a multicenter, 4-arm, randomized, parallel-group study evaluating the safety and tolerability of adjunctive BRV treatment administered as intravenous (iv) infusion or iv bolus in subjects with localization-related or generalized epilepsy from 16 to 70 years old.**

N01379 will explore the long-term safety and efficacy of BRV in subjects with epilepsy while providing access to BRV for subjects who may benefit from open-label treatment with BRV.

#### Change #9

### Section 3.1 Primary objective

#### Original text

The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in focal epilepsy subjects.

**Has been changed to:**

The primary objective is to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200mg/day in epilepsy subjects.

**Change #10**

**Section 3.3 Exploratory objectives**

**Original text**

- To explore the effects of BRV on subjects' HRQoL
- To explore direct medical resource use
- To explore any change in socio-professional status

**Has been changed to:**

- To explore the effects of BRV on subjects' HRQoL
- To explore direct medical resource use
- To explore any change in socio-professional status
- **To assess the role of gene variants of SV2 in affecting response to BRV (as part of a DNA analysis at the program level)**

**Change #11**

**Section 4.1.2 Secondary efficacy variables**

**Original text**

Secondary efficacy variables are as follows:

- Seizure frequency per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Responder rate in POS (type I) by 3-month periods over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

**Has been changed to:**

Secondary efficacy variables are as follows:

- Seizure frequency per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Responder rate in POS (type I) by 3-month periods over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

**Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.**

#### **Change #12**

#### **Section 4.1.3 Other efficacy variables**

##### **Original text**

The other efficacy variables are as follows:

- Change in QOLIE-31-P scores from the Baseline of N01358 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in HADS scores from the Baseline of N01358 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Medical resources use during the first 2 years of the Evaluation Period
- Change in socio-professional data from the Baseline of N01358 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

**Has been changed to:**

##### **4.1.3.1 Seizure-related other efficacy variables**

For subjects from N01258 with generalized epilepsy:

- **Generalized (type II) seizure days standardized to a 28-day duration by 3-month periods over the Evaluation Period**
- Seizure days per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

**Some variables may not be assessed if the number of subjects with generalized epilepsy is insufficient.**

##### **4.1.3.2 Nonseizure-related other efficacy variables**

The other efficacy variables are as follows:

- Medical resources use during the first 2 years of the Evaluation Period

- Change in QOLIE-31-P scores from the Baseline of **N01358 or N01258** to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in HADS scores from the Baseline of **N01358 or N01258** to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in socio-professional data from the Baseline of **N01358 or N01258** to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

### Change #13

#### Section 4.2 Safety variables

##### Original text

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

##### Has been changed to:

- AEs
- Laboratory tests (including hematology, blood chemistry, urinalysis, and pregnancy test, and **additional endocrinology once a year**)
- ECG
- Physical examination
- Neurological examination
- Vital signs
- Body weight

### Change #14

#### Section 5.1 Study description, paragraph 1

##### Original text

This is a Phase 3, open-label, LTFU, multicenter, noncomparative, and single-arm study. The subject population will be adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized. Subjects under 18 years may be included only where legally permitted and ethically accepted. Subjects must complete the Treatment Period of N01358 prior to

enrollment into N01379. Upon completion or early discontinuation from N01379, there will be a Down-Titration Period, followed by a Posttreatment Period during which the subject will not receive study drug.

**Has been changed to:**

This is a Phase 3, open-label, LTFU, multicenter, noncomparative, and single-arm study. The subject population will be adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized **from N01358 and subjects with localization-related or generalized epilepsy from N01258**. Subjects under 18 years may be included only where legally permitted and ethically accepted. Subjects must complete the Treatment Period of N01358 **or the Evaluation Period of N01258** prior to enrollment into N01379. Upon completion or early discontinuation from N01379, there will be a Down-Titration Period, followed by a Posttreatment Period during which the subject will not receive study drug.

**Change #15**

**Section 5.1 Study description, paragraph 3**

**Original text**

Subjects will be started on oral BRV at a dose of 150mg/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. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study and must always be administered as a symmetrical morning and evening dose.

**Has been changed to:**

Subjects **from N01358** will be started on oral BRV at a dose of 150mg/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 N01258 will be started at an oral dose of BRV 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment.** The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study and must always be administered as a symmetrical morning and evening dose.

**Change #16**

**Section 5.1.1 Study duration per subject**

**Original text**

Subject recruitment for the study will begin in approximately Q1 2011. For each subject, the study will last from study entry until either regulatory approval of BRV has been granted by any Health Authority in an indication of adjunctive treatment of POS, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

**Has been changed to:**



Subject recruitment for the study will begin in approximately Q2 2011. For each subject, the study will last from study entry until either regulatory approval of BRV has been granted by any Health Authority in an indication of adjunctive treatment of POS, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

#### **Change #17**

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

###### **Original text**

It is estimated that approximately 650 to 720 subjects will enter the study, based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379.

It is estimated that 120 sites will participate in the study.

###### **Has been changed to:**

It is estimated that approximately 650 to 720 subjects **from N01358** will enter the study, based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. **Up to 100 subjects from N01258 may also be eligible for enrollment.**

It is estimated that 120 sites from N01358 and up to 25 sites from N01258 will participate in the study.

#### **Change #18**

##### **Section 5.1.3 Anticipated regions and countries**

###### **Original text**

The regions and countries for enrollment will be the same as the core study, N01358. The study is planned to be performed in North America (Canada and USA), Western Europe, Latin America, Eastern Europe, Asia, and Africa, with possible extension to other countries or regions.

###### **Has been changed to:**

The regions and countries for enrollment will be the same as in the **previous studies, N01358 and N01258. N01358** is planned to be performed in North America (Canada and USA), Western Europe, Latin America, Eastern Europe, Asia, and Africa, **and N01258 is planned to be performed in the USA and Europe**, with possible extension to other countries or regions **for both studies.**



**Change #19**

**Section 5.2 Schedule of study assessments, Table 5:1.**

The following rows have been added

Written Informed Consent for DNA analysis (for subjects from N01358)	X								<u>13.1</u>	
Blood sampling for the DNA analysis <sup>i</sup>	X								<u>10.4.2</u>	

## Change #20

### Section 5.2 Schedule of study assessments, Table 5:1., abbreviations

#### Original text

AE=adverse event; AED=antiepileptic drug; CRF=Case Report Form; DTP=Down-Titration Phone Call; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; HADS=Hospital Anxiety and Depression Scale; IVRS=interactive voice response system; M=Month; MEV=Minimal Evaluation Visit; NA=not applicable; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory; V=Visit; YEV=Yearly Evaluation Visit

#### Has been changed to:

AE=adverse event; AED=antiepileptic drug; CRF=Case Report Form;  
**DNA=deoxyribonucleic acid**; DTP=Down-Titration Phone Call; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; HADS=Hospital Anxiety and Depression Scale; IVRS=interactive voice response system; M=Month; MEV=Minimal Evaluation Visit; NA=not applicable; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory; V=Visit; YEV=Yearly Evaluation Visit

## Change #21

### Section 5.2 Schedule of study assessments, Table 5:1., footnotes

#### Original text

Note: Months and visit numbers are displayed for the first 2 years. The visit schedule described in Section 5.3 will be applied.

Note: At the EV, the IVRS call will be part of the N01358 final visit.

- a. The Down-Titration Phone Call at the end of the Down-Titration Period is mandatory.
- b. General medical and procedures history, AED history, recording of seizures, and epilepsy history will be obtained from the Baseline of N01358 and do not need to be recorded on the CRF for this study.
- c. The following will be obtained from the last visit of N01358 and do not need to be recorded on the CRF for this study: physical and neurological examination, vital signs, hospital stays, healthcare provider consultations not foreseen by the protocol, ECG, and laboratory assessments (hematology, blood chemistry, and urinalysis).
- d. Height will be obtained at Visit 1 in N01358.
- e. At the FV, an ECG is mandatory, except if the FV follows an EDV where ECG results were normal.
- f. QOLIE-31-P and HADS are to be completed at the beginning of the visit by all subjects who are able to complete the assessments on their own. These will be collected only for the first 2 years.

g. Socio-professional data, hospital stays, and healthcare provider consultations not foreseen by the protocol will be collected for all subjects for the first 2 years.

h. Laboratory assessment includes hematology, blood chemistry, and urinalysis; where applicable (women with childbearing potential), a urine pregnancy test will be done. Laboratory 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.

i. Ongoing AEs at the time of subject completion of N01358 will be obtained from the database for N01358 and should not be recorded on the CRF for N01379 unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the CRF for N01379 with the onset date corresponding to the date of change in condition.

j. Ongoing medications (AEDs and non-AEDs) at the time of subject completion of N01358 will be obtained from the database for N01358 and should not be recorded on the CRF for N01379 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the CRF for N01379 with the start date corresponding to the date of change in administration.

k. End of study status will be completed at the FV for subjects having performed an EDV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects).

#### **Has been changed to:**

Note: Months and visit numbers are displayed for the first 2 years. The visit schedule described in Section 5.3 will be applied.

Note: At the EV, the IVRS call will be part of the N01358 **or** N01258 final visit.

a. The Down-Titration Phone Call at the end of the Down-Titration Period is mandatory.

b. General medical and procedures history, AED history, recording of seizures, and epilepsy history will be obtained from the Baseline of N01358 **or** N01258 and do not need to be recorded on the CRF for this study.

c. The following will be obtained from the last visit of N01358 **or** N01258 and do not need to be recorded on the CRF for this study: physical and neurological examination, vital signs, hospital stays, healthcare provider consultations not foreseen by the protocol, ECG, and laboratory assessments (hematology, blood chemistry, and urinalysis).

d. Height will be obtained at Visit 1 in N01358 **or** N01258.

e. At the FV, an ECG is mandatory, except if the FV follows an EDV where ECG results were normal.

f. QOLIE-31-P and HADS are to be completed at the beginning of the visit by all subjects who are able to complete the assessments on their own. These will be collected only for the first 2 years.

g. Socio-professional data, hospital stays, and healthcare provider consultations not foreseen by the protocol will be collected for all subjects for the first 2 years.

- h. Laboratory assessment includes hematology, blood chemistry, and urinalysis; where applicable (women with childbearing potential), a urine pregnancy test will be done. **Endocrinology will be assessed at each YEIV. In addition, liver function tests as described in Section 10.5.1 will be performed at the MEV in M3 and M9.** Laboratory 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.
- i. **The DNA analysis is part of N01379 and will be performed only in adult subjects from N01358 after signing an additional Informed Consent form and where ethically accepted and authorized by regulatory agencies. Mentally impaired subjects will be excluded from the DNA analysis.**
- j. Ongoing AEs at the time of subject completion of N01358 **or N01258** will be obtained from the database for N01358 **or N01258** and should not be recorded on the CRF for N01379 unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the CRF for N01379 with the onset date corresponding to the date of change in condition.
- k. Ongoing medications (AEDs and non-AEDs) at the time of subject completion of N01358 **or N01258** will be obtained from the database for N01358 **or N01258** and should not be recorded on the CRF for N01379 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the CRF for N01379 with the start date corresponding to the date of change in administration.
- l. End of study status will be completed at the FV for subjects having performed an EDV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects).

## Change #22

### Section 5.3 Visit schedule, Table 5:2.

#### Original text

A full visit schedule is presented in the following table.

**Table 5:2. Visit schedule**

First year follow-up		
Month	Visit	Type of visit
M0	V1	EV
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV
M4	-	-
M5	-	-
M6	V5	FEV

**Table 5:2. Visit schedule**

First year follow-up		
Month	Visit	Type of visit
M7	-	-
M8	-	-
M9	V6	MEV
M10	-	-
M11	-	-
Second year follow-up <sup>a</sup>		
Month	Visit	Type of visit
M12	V7	YEV
M15	V8	MEV
M18	V9	FEV
M21	V10	MEV
EV=Entry Visit; FEV=Full Evaluation Visit; M=month; MEV=Minimal Evaluation Visit; V=Visit; YEV=Yearly Evaluation Visit		
Note: “-” denotes that no visit is scheduled in that month.		
<sup>a</sup> . Subsequent years will follow the same visit schedule.		

**Has been changed to:**

A full visit schedule is presented in the following table.

**Table 5:2. Visit schedule**

First year follow-up		
Month	Visit	Type of visit
M0	V1	EV
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV <sup>b</sup>
M4	-	-
M5	-	-
M6	V5	FEV
M7	-	-
M8	-	-

**Table 5:2. Visit schedule**

First year follow-up		
M9	V6	MEV <sup>b</sup>
M10	-	-
M11	-	-
Second year follow-up <sup>a</sup>		
Month	Visit	Type of visit
M12	V7	YEV
M15	V8	MEV
M18	V9	FEV
M21	V10	MEV
EV=Entry Visit; FEV=Full Evaluation Visit; M=month; MEV=Minimal Evaluation Visit; V=Visit; YEV=Yearly Evaluation Visit		
Note: “-” denotes that no visit is scheduled in that month.		
<sup>a</sup> Subsequent years will follow the same visit schedule.		
<sup>b</sup> Liver function tests will be performed in addition to the assessments described in Section 8.3		

**Change #23****Section 5.4 Rationale for study design and selection of dose****Original text**

In the prerequisite study (N01358) for inclusion in N01379, subjects will be randomized to BRV 100mg/day, BRV 200mg/day or to matching PBO. Previous Phase 2/3 clinical studies in POS and dose-response modeling suggest that optimal seizure frequency requires BRV doses of 50 to 100mg/day, with BRV 150mg/day possibly providing some additional benefit. Following consultation with regulatory authorities, it was recommended to also explore BRV 200mg/day to obtain data on the upper end of the dose response curve in N01358.

Subjects will enter N01379 at a dose of BRV 150mg/day (2 equally divided doses administered twice daily). In Phase 2/3 studies for POS with BRV doses up to 150mg/day, the overall discontinuation rate and the discontinuation rate due to TEAEs was low and similar to PBO. The most frequently reported TEAEs at BRV doses up to 150mg/day were headache, somnolence, dizziness, and fatigue. 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.

**Has been changed to:**

In the **previous** study N01358, subjects will be randomized to **an oral dose of** BRV 100mg/day, BRV 200mg/day, or to matching PBO. **In the previous study N01258, subjects will receive either a 60-second iv bolus or a 15-minute iv infusion at a dose of BRV 100mg twice daily (200mg/day).** Previous Phase 2/3 clinical studies in POS and

dose-response modeling suggest that optimal seizure frequency requires BRV doses of 50 to 100mg/day, with BRV 150mg/day possibly providing some additional benefit. Following consultation with regulatory authorities, it was recommended to also explore BRV 200mg/day to obtain data on the upper end of the dose response curve in N01358.

**The starting doses in N01379 will be BRV 150mg/day for subjects from N01358 and BRV 200mg/day for subjects from N01258. The study entry doses will be taken as 2 equally divided oral doses administered twice daily. In Phase 2/3 studies for POS with BRV doses up to 150mg/day, the overall discontinuation rate and the discontinuation rate due to TEAEs was low and similar to PBO. The most frequently reported TEAEs at BRV doses up to 150mg/day were headache, somnolence, dizziness, and fatigue. 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.**

#### **Change #24**

##### **Section 6.1 Inclusion criteria, bullets 1 and 3**

###### **Original text**

1. An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved written informed consent signed and dated by the subject or by parent(s) or legally acceptable representative. The consent form or a specific assent form, where required, will be signed and dated by minors.
2. Subject completed the Treatment Period of N01358.

###### **Has been changed to:**

1. An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved written informed consent signed and dated by the subject or by parent(s) or legally acceptable representative. The consent form or a specific assent form, where required, will be signed and dated by minors. **In countries and sites where a DNA analysis is accepted, an additional Informed Consent form will have to be signed by subjects coming from N01358. Deoxyribonucleic acid analysis will be performed only in adults, and the subject can withdraw consent to the use of the sample at any time. Mentally impaired subjects will be excluded. In case the consent is withdrawn, the site must request the destruction of the sample.**
2. Subject completed the Treatment Period of N01358 or the Evaluation Period of N01258.

#### **Change #25**

##### **Section 6.2 Exclusion criteria, bullets 1 and 3**

###### **Original text**

1. Subject has developed hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs as stated in this protocol during the course of the core study
2. Poor compliance with the visit schedule or medication intake in the previous BRV study

###### **Has been changed to:**



1. Subject has developed hypersensitivity to any components of the investigational medicinal product (IMP) or comparative drugs as stated in this protocol during the course of the core studies
2. Poor compliance with the visit schedule or medication intake in the previous BRV studies

#### **Change #26**

#### **Section 6.3 Withdrawal criteria, paragraph 1**

##### **Original text**

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

##### **Has been changed to:**

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. **Subjects who have signed an additional Informed Consent form for DNA analysis may withdraw their consent to the DNA analysis at any time and may continue their participation in the N01379 study.**

#### **Change #27**

#### **Section 7.2 Treatments to be administered, paragraph 1**

##### **Original text**

Subjects will be started on a BRV dose of 150mg/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. The BRV dose can subsequently be adjusted based on the individual subject's seizure control and/or tolerability. However, the BRV dose should not exceed 200mg/day during the study.

##### **Has been changed to:**

Subjects **from N01358** will be started on a BRV dose of 150mg/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 N01258 will be started at a BRV dose of 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks, unless the subject is not able to tolerate treatment.** The BRV dose can subsequently be adjusted based on the individual subject's seizure control and/or tolerability. However, the BRV dose should not exceed 200mg/day during the study.

#### **Change #28**

#### **Section 7.3 Packaging, paragraph 1**

##### **Original text**

Oral tablets of BRV 10mg, 25mg, and 50mg will be packaged in high density polyethylene bottles of 200 tablets. Each container will have an unique, preprinted identification number.

**Has been changed to:**

Oral tablets of BRV 25mg and 50mg will be packaged in high density polyethylene bottles of 200 tablets, **and the 10mg tablets will be packaged in bottles containing 38 tablets.** Each container will have a unique, preprinted identification number.

**Change #29**

**Section 7.8.2 Prohibited concomitant treatments (medications and therapies)**

**Original text**

The following concomitant AED medications are prohibited during the study:

- Felbamate (except if on stable dose during previous double-blind study N01358)
- Vigabatrin

**Has been changed to:**

The following concomitant AED medications are prohibited during the study:

- Felbamate (except if on stable dose during previous studies **N01358 and N01258**)
- Vigabatrin

**Change #30**

**Section 7.9 Blinding**

**Original text**

This is an open-label LTFU study of the preceding double-blind study N01358.

**Has been changed to:**

This is an open-label LTFU study of the preceding double-blind study N01358 **and of the open-label randomized study N01258.**

**Change #31**

**Section 7.10 Randomization and numbering of subjects**

**Original text**

Since N01379 is an open-label LTFU study of the preceding double-blind study N01358, subjects will not be randomized to any treatment groups. All subjects enrolled will start with a dose of BRV 150mg/day and will be maintained on that dose for at least 2 weeks, unless they are unable to tolerate the dose.

Subjects will continue with the 5-digit subject numbers assigned by the interactive voice response system (IVRS) in the preceding double-blind study N01358.

**Has been changed to:**

Since N01379 is an open-label LTFU study **for** N01358 and N01258; subjects will not be randomized to any treatment groups. Subjects **from N01358** will start with a dose of BRV 150mg/day and will be maintained on that dose for at least 2 weeks, unless they are unable to tolerate the dose. **Subjects from N01258 will start at a dose of BRV 200mg/day and**

**should be maintained on that dose for at least 2 weeks unless they are unable to tolerate the dose.**

Subjects will continue with the 5-digit subject numbers assigned by the interactive voice response system (IVRS) in the preceding studies.

#### **Change #32**

### **Section 8 STUDY PROCEDURES BY VISIT**

#### **Original text**

Prior to any study activities, the subject or legal representative will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with regulatory requirements. The subject or legal representative will be given adequate time to consider any information concerning the study, given to them by the Investigator or designee. As part of the informed consent procedure, subject or legal representative will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study. Additionally, if applicable (according to subject's age and local requirements), the subject will sign an IRB/IEC assent form.

#### **Has been changed to:**

Prior to any study activities, the subject or legal representative will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with regulatory requirements. **Subjects from N01358 agreeing to the DNA analysis will have to sign an additional Informed Consent form.** The subject or legal representative will be given adequate time to consider any information concerning the study, given to them by the Investigator or designee. As part of the informed consent procedure, **the** subject or legal representative will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study. Additionally, if applicable (according to **the** subject's age and local requirements), the subject will sign an IRB/IEC assent form.

#### **Change #33**

### **Section 8.1 Entry Visit**

#### **Original text**

- Written Informed Consent
- Subject identification card dispensing
- Verification inclusion/exclusion criteria
- Demographic data
- Childbearing potential
- Weight
- IVRS call
- Daily record card (DRC) dispensed
- Medical procedures

- Concomitant AED
- Concomitant non-AED

Ongoing medications (AEDs and non-AEDs) at the time of subject completion of N01358 will be obtained from the database for N01358 and should not be recorded on the CRF for N01379 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the CRF for N01379 with the start date corresponding to the date of change in administration.

- Recording of AEs

Ongoing AEs at the time of subject completion of N01358 will be obtained from the database for N01358 and should not be recorded on the CRF for N01379 unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the CRF for N01379 with the onset date corresponding to the date of change in condition.

- Drug dispensing
- Appointment for the next visit according to the schedule described in (Section 5.3)

The following data will be obtained from the Baseline of N01358 and do not need to be recorded on the CRF for this study.

- General medical and procedures history
- AED history
- Recording of seizures
- Epilepsy history

The following data will be obtained from the last visit of N01358 and do not need to be recorded on the CRF for this study.

- Vital signs
- Neurological examination
- Physical examination
- ECG
- Laboratory assessments
- Hospital stays
- Healthcare provider consultations not foreseen by the protocol

Height will be obtained from Visit 1 in N01358.

**Has been changed to:**

- Written Informed Consent
- **Additional written Informed Consent for subjects agreeing to DNA analysis**
- Subject identification card dispensing

- Verification inclusion/exclusion criteria
- Demographic data
- Childbearing potential
- Weight
- IVRS call
- Daily record card (DRC) dispensed
- Medical procedures
- **Blood sampling for the DNA analysis for consenting subjects coming from N01358. The DNA analysis will be performed in adult subjects where ethically accepted and authorized by regulatory agencies.**
- Concomitant AED
- Concomitant non-AED

Ongoing medications (AEDs and non-AEDs) at the time of subject completion of N01358 or N01258 will be obtained from the database for N01358 or N01258 and should not be recorded on the CRF for N01379 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded on the CRF for N01379 with the start date corresponding to the date of change in administration.

- Recording of AEs

Ongoing AEs at the time of subject completion of N01358 or N01258 will be obtained from the database for N01358 or N01258 and should not be recorded on the CRF for N01379 unless there is a change in intensity or seriousness. In this event, the AE should be recorded on the CRF for N01379 with the onset date corresponding to the date of change in condition.

- Drug dispensing
- Appointment for the next visit according to the schedule described in (Section 5.3)

The following data will be obtained from the Baseline of N01358 or N01258 and do not need to be recorded on the CRF for this study.

- General medical and procedures history
- AED history
- Recording of seizures
- Epilepsy history

The following data will be obtained from the last visit of N01358 or N01258 and do not need to be recorded on the CRF for this study.

- Vital signs
- Neurological examination

- Physical examination
- ECG
- Laboratory assessments
- Hospital stays
- Healthcare provider consultations not foreseen by the protocol

Height will be obtained from Visit 1 in N01358 **or** N01258.

#### **Change #34**

### **Section 8.3 Minimal Evaluation Visit**

#### **Original text**

- Vital signs
- IVRS call
- DRC dispensed
- DRC retrieved
- Recording of seizures
- Hospital stays (for the first 2 years)
- Healthcare provider consultations not foreseen by the protocol (for the first 2 years)
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing
- Drug return/accountability
- Appointment for the next visit according to the schedule described in Section 5.3

#### **Has been changed to:**

- Vital signs
- IVRS call
- DRC dispensed
- DRC retrieved
- Recording of seizures
- Hospital stays (for the first 2 years)
- Healthcare provider consultations not foreseen by the protocol (for the first 2 years)

- **Liver function tests will be performed in Month 3 (V4) and Month 9 (V6) as described in Section 10.5.1**
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing
- Drug return/accountability
- Appointment for the next visit according to the schedule described in Section 5.3

#### **Change #35**

#### **Section 8.4 Yearly Evaluation Visit, bullet on laboratory assessments**

##### **Original text**

- Laboratory assessments

##### **Has been changed to:**

- Laboratory assessments, including thyroid-stimulating hormone (TSH) assessments

#### **Change #36**

#### **Section 9.1.1 QOLIE-31-P scores, paragraph 1**

##### **Original text**

The QOLIE-31-P - Version 2.0 US - English (see Section 16.1) will be used to evaluate the HRQoL of study subjects (Cramer and Van Hammée, 2003).

##### **Has been changed to:**

The QOLIE-31-P - Version 2.0 (see Section 16.1) will be used to evaluate the HRQoL of study subjects (Cramer and Van Hammée, 2003).

#### **Change #37**

#### **Section 9.1.5 Healthcare provider consultations not foreseen by the protocol**

##### **Original text**

At the FEV, MEV, YEV, Last Evaluation Period Visit, and EDV, healthcare provider consultations not foreseen by the protocol will be recorded in the CRF. It will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation. At the EV, data will be obtained from the last visit of the previous study, N01358 and do not need to be recorded on the CRF for this study. Healthcare provider consultations not foreseen by the protocol will be recorded for the first 2 years.



### Has been changed to:

At the FEV, MEV, YEV, Last Evaluation Period Visit, and EDV, healthcare provider consultations not foreseen by the protocol will be recorded in the CRF. It will include the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation. At the EV, data will be obtained from the last visit of the previous study, N01358 **or N01258**, and do not need to be recorded on the CRF for this study. Healthcare provider consultations not foreseen by the protocol will be recorded for the first 2 years.

### Change #38

#### Section 9.1.6 Hospital stays

##### Original text

At the FEV, MEV, YEV, Last Evaluation Period Visit, and EDV, data on hospital stays will be collected in the CRF. It will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay. At the EV, data will be obtained from the last visit of the previous study, N01358 and do not need to be recorded on the CRF for this study. Hospital stays will be recorded for the first 2 years.

### Has been changed to:

At the FEV, MEV, YEV, Last Evaluation Period Visit, and EDV, data on hospital stays will be collected in the CRF. It will include the reason leading to the hospitalization, the admission ward, transfers, and length of stay. At the EV, data will be obtained from the last visit of the previous study, N01358 **or N01258**, and do not need to be recorded on the CRF for this study. Hospital stays will be recorded for the first 2 years.

### Change #39

#### Section 10.4 Laboratory measurements

##### Original text

Laboratory assessments (including hematology, blood chemistry, and urinalysis) will be conducted using standard methods at a central laboratory. 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 11mL per sampling, which includes 3mL for hematology and 8mL for blood chemistry.

The subject must be preferably fasting, but study medication intake must not be delayed.

The following laboratory assessments will be conducted:

Hematology	Blood chemistry	Urinalysis	Pregnancy
WBC	Glucose	Glucose	β-hCG
RBC	Sodium	Ketones	

Hematology	Blood chemistry	Urinalysis	Pregnancy
Hemoglobin	Potassium	Occult blood	
Hematocrit	Calcium	Protein	
MCV	Chloride	Nitrites	
MCH	Bicarbonate	Leukocytes	
MCHC	Phosphorus (inorganic)	Microscopic exam <sup>a</sup>	
Platelet count	Total protein		
Lymphocytes (number, %)	Albumin		
Monocytes (number, %)	Total bilirubin		
Neutrophils (number, %)	Alkaline phosphatase		
Eosinophils (number, %)	AST (SGOT)		
Basophils (number, %)	ALT (SGPT)		
	GGT		
	Uric acid		
	Urea		
	Creatinine		
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); β-hCG=beta-human chorionic gonadotropin; GGT=gamma-glutamyltransferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cells; WBC=white blood cells <sup>a</sup> Including bacteria, cells, casts, and crystals will be performed for all samples.			

**Has been changed to:**

#### **10.4.1 Safety laboratory assessments**

Laboratory assessments (including hematology, blood chemistry, endocrinology, and urinalysis) will be conducted using standard methods at a central laboratory. 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 11mL per sampling, which includes 3mL for hematology and 8mL for blood chemistry. In addition, a 10mL blood sample for the DNA analysis will be collected at the EV in consenting adult subjects from N01358.

The subject must be preferably fasting, but study medication intake must not be delayed.

The following laboratory assessments will be conducted:

Hematology	Blood chemistry	Urinalysis	Endo- crinology	Pregnancy
WBC	Glucose	Glucose	TSH <sup>a</sup>	β-hCG
RBC	Sodium	Ketones		
Hemoglobin	Potassium	Occult blood		
Hematocrit	Calcium	Protein		
MCV	Chloride	Nitrites		
MCH	Bicarbonate	Leukocytes		
MCHC	Phosphorus (inorganic)	Microscopic exam <sup>b</sup>		
Platelet count				
Lymphocytes (number, %)	Total protein			
Monocytes (number, %)	Albumin			
Neutrophils (number, %)	Total bilirubin <sup>c</sup>			
Eosinophils (number, %)	Alkaline phosphatase <sup>c</sup>			
Basophils (number, %)				
	AST (SGOT) <sup>c</sup>			
	ALT (SGPT) <sup>c</sup>			
	GGT <sup>c</sup>			
	Uric acid			
	Urea			
	Creatinine			
<p>ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); β-hCG=beta-human chorionic gonadotropin; GGT=gamma-glutamyltransferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; <b>MEV=Minimal Evaluation Visit</b>; RBC=red blood cells; <b>TSH=thyroid-stimulating hormone</b>; WBC=white blood cells; <b>YEV=Yearly Evaluation Visit</b></p> <p><sup>a</sup> <b>Thyroid-stimulating hormone will be assessed at each YEV.</b></p> <p><sup>b</sup> Including bacteria, cells, casts, and crystals will be performed for all samples.</p> <p><sup>c</sup> <b>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></p>				

#### Change #40

#### Section 10.4 Laboratory measurements, last 2 paragraphs

##### Original text

Laboratory safety assessments at the EV will be taken from the last visit of N01358 and do not need to be recorded on the CRF. Thereafter, laboratory safety assessments will be

performed at the FEV, YEV, Last Evaluation Period Visit, and EDV. Laboratory assessments will also be mandatory at the FV, except if the FV follows an EDV where laboratory results were normal.

Results for hematology, blood chemistry, urinalysis, and pregnancy tests will be provided by fax to the Investigator within 72 hours after sample receipt. Results will be reported by the central laboratory to the Investigator as exact values, with a flag to those values that are outside the therapeutic range.

**Has been changed to:**

#### **10.4.1 Safety laboratory assessments**

Laboratory safety assessments at the EV will be taken from the last visit of N01358 or N01258 and do not need to be recorded on the CRF. Thereafter, laboratory safety assessments will be performed at the FEV, YEV, Last Evaluation Period Visit, and EDV. In addition, liver function tests will be performed at MEVs (Visit 4 and Visit 6) during the first year. Endocrinology (TSH) measurements will be performed at YEVs only. Laboratory assessments will also be mandatory at the FV, except if the FV follows an EDV where laboratory results were normal.

Results for hematology, blood chemistry, urinalysis, endocrinology, and pregnancy tests will be provided by fax to the Investigator within 72 hours after sample receipt. Results will be reported by the central laboratory to the Investigator as exact values, with a flag to those values that are outside the therapeutic range.

**Change #41**

**The following paragraph has been added to Section 10.4.**

#### **Section 10.4.2 DNA analysis**

**For subjects coming from N01358, a blood sample for DNA analysis will be collected at the EV in order to explore a possible correlation between the SV2 gene variations and the subject's response to BRV. Blood samples for DNA analysis will be collected only in adults where ethically accepted and authorized by legal authorities. The DNA analysis will be done in a separate report at the program level.**

Samples will be split into 2 aliquots and will be initially stored at the central laboratory and will then be shipped to the genotyping facility for DNA extraction and genotyping. Samples will be stored at -20°C for a period of up to 20 years.

**Change #42**

#### **Section 10.5.3 Body weight and height**

**Original text**

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram or pound) will be measured at the EV, FEV, YEV, Last Evaluation Period Visit, EDV, and FV. Height will be obtained from Visit 1 in N01358.

**Has been changed to:**

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram or pound) will be measured at the EV, FEV, YEV, Last Evaluation Period Visit, EDV, and FV. Height will be obtained from Visit 1 in N01358 or N01258.

**Change #43**

**Section 12.1 Definition of analysis populations**

**Original text**

The Efficacy Population will consist of all subjects who took at least 1 dose of study medication and have at least 1 seizure diary during the Evaluation Period.

The Safety Population will consist of all subjects who took at least 1 dose of study medication.

**Has been changed to:**

Efficacy Populations will consist of all subjects who took at least 1 dose of study medication and have at least 1 seizure diary during the Evaluation Period. **Separate Efficacy Populations will be defined for subjects with POS and subjects with generalized epilepsy.**

The Safety Population will consist of all subjects who took at least 1 dose of study medication.

**Change #44**

**Section 12.3.2 Analysis of the secondary efficacy variables**

**Original text**

The following secondary efficacy variables will be summarized with descriptive statistics.

- Seizure frequency per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Responder rate in POS (type I) by 3-month periods over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

**Has been changed to:**

The following secondary efficacy variables will be summarized with descriptive statistics.

- Seizure frequency per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Responder rate in POS (type I) by 3-month periods over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

**Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.**

#### **Change #45**

### **Section 12.3.3 Analysis of the other efficacy variables**

#### **Original text**

The following other efficacy variables will be summarized with descriptive statistics.

- Change in QOLIE-31-P scores from the Baseline of N01358 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in HADS scores from the Baseline of N01358 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Medical resources use during the first 2 years of the Evaluation Period
- Change in socio-professional data from the Baseline of N01358 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

#### **Has been changed to:**

##### **12.3.3.1 Seizure-related other efficacy variables**

For subjects from N01258 with generalized epilepsy:

- **Generalized (type II) seizure days standardized to a 28-day duration by 3-month periods over the Evaluation Period**
- Seizure days per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

**Some variables may not be assessed if the number of subjects with generalized epilepsy is insufficient.**

##### **12.3.3.2 Nonseizure-related other efficacy variables**

The following other efficacy variables will be summarized with descriptive statistics.



- Medical resources use during the first 2 years of the Evaluation Period
- Change in QOLIE-31-P scores from the Baseline of N01358 **or N01258** to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in HADS scores from the Baseline of N01358 **or N01258** to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in socio-professional data from the Baseline of N01358 **or N01258** to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

#### Change #46

### Section 12.8 Determination of sample size

#### Original text

For this open-label LTFU, 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 650 to 720 subjects will enter the study based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379.

#### Has been changed to:

For this open-label LTFU, no sample size calculation will be performed. The sample size will depend upon recruitment into and completion of the previous studies. It is estimated that approximately 650 to 720 subjects **from N01358** will enter the study based on the assumption that at least 90% of randomized subjects from N01358 will complete N01358 and enroll in N01379. **Up to 100 subjects from N01258 may also be eligible.**

#### Change #47

### Section 13.1 Informed consent, paragraph 3

#### Original text

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

#### Has been changed to:

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). **An additional written Informed Consent form should be signed and dated for adult subjects from N01358 (without mental impairment) giving their consent to blood sampling for DNA analysis.** The subject or his/her legal representative must receive a copy of the signed and dated



Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

#### **Change #48**

### **Section 15 REFERENCES**

The following reference was added.

**Goldstein DB, Need AC, Singh R, Sisodiya SM. Potential genetic causes of heterogeneity of treatment effects. T Am J Med. 2007;120(Suppl 1):S21-5.**

## **16.4 Protocol Amendment 2**

### **Rationale for the amendment**

The main reasons for this protocol amendment are as follows:

- Procedures for reporting SAEs were updated to implement the Food and Drug Administration (FDA) Final Rule requirements.
- The C-SSRS was added to address the requirement of the FDA that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indications.
- The study variables were rearranged to more appropriately show that the main purpose of N01379 is to evaluate long-term safety of BRV in this patient population. The HADS scores subsection was moved from Section 9 Assessment of Efficacy to Section 10 Assessment of Safety and the statistical analysis section (Section 12) was updated to be consistent with the rearrangement of the study variables.

In addition, there were a few changes made to the protocol to update and clarify information, such as an update to the SAE reporting phone and fax numbers for the US and Canada.

### **Modifications and changes**

#### **Global changes**

The following changes were made throughout the protocol:

- Inclusion of a suicidality assessment using the C-SSRS at each visit in response to the US FDA request. In addition, the exclusion and withdrawal criteria were updated to include the C-SSRS assessment.
- Inclusion of the list of Anticipated SAEs in Section 10.4 in response to the US FDA Final Rule. Due to this addition, subsequent sections within Section 10 were renumbered accordingly.

## Specific changes

### Change #1

#### Original title:

AN OPEN-LABEL, MULTICENTER, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN SUBJECTS AGED 16 YEARS OR OLDER WITH PARTIAL ONSET SEIZURES

#### 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 AGED 16 YEARS OR OLDER WITH EPILEPSY

### Change #2

The clinical trial biostatistician was changed from [REDACTED] in both the SPONSOR DECLARATION and STUDY CONTACT INFORMATION sections.

### Change #3

#### SERIOUS ADVERSE EVENT REPORTING

#### Original table:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding		
<b>Fax</b>	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 21 USA and Canada: +1 800 880 6949 or +1 866 890 3175 Japan: +81 3 5283 1869	
<b>Phone</b>	<b>During business hours:</b>	<b>Outside business hours:</b>
	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 68 USA and Canada: +1 919 767 2627 Japan: +81 3 5283 1814	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 68 USA and Canada: +1 404 895 0794 Japan: +81 80 1100 5372

**Has been changed to:**

<b>Serious adverse event reporting (24h), safety related issues, and emergency unblinding</b>		
<b>Fax</b>	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 21 USA: +1 800 880 6949 Canada: +1 877 582 8842 Japan: +81 3 5283 1869	
<b>Phone</b>	<b>During business hours:</b>	<b>Outside business hours:</b>
	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 68 USA and Canada: +1 404 895 0794 Japan: +81 3 5283 1814	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 68 USA and Canada: +1 404 895 0794 Japan: +81 80 1100 5372

**Change #4**

**List of abbreviations**

The following abbreviations were added to the list:

C-SSRS      Columbia-Suicide Severity Rating Scale

FDA          Food and Drug Administration

**Change #5**

**Section 1 Summary**

**Original text:**

Paragraphs 7 and 8:

Other nonseizure-related efficacy variables include the Patient Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P) scores, the Hospital Anxiety and Depression Scale (HADS) scores, medical resources use, and socio-professional data during the first 2 years of the Evaluation Period.

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

### Has been changed to:

Other efficacy **and pharmacoeconomic** variables include the Patient Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P) scores, medical resources use, and socio-professional data during the first 2 years of the Evaluation Period.

Safety variables include adverse events (AEs), laboratory tests (hematology, blood chemistry, urinalysis, endocrinology, and pregnancy test), electrocardiogram (ECG), vital signs, physical and neurological examinations, **the Hospital Anxiety and Depression Scale (HADS) scores**, and body weight.

### Change #6

## Section 4 STUDY VARIABLES

### Original Sections:

#### 4.1 Efficacy variables

##### 4.1.1 Primary efficacy variable

The primary efficacy variable is the POS (type I) seizure frequency standardized to a 28-day duration. This will be summarized by 3-month periods over the Evaluation Period.

##### 4.1.2 Secondary efficacy variables

Secondary efficacy variables are as follows:

- Seizure frequency per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Responder rate in POS (type I) by 3-month periods over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.

##### 4.1.3 Other efficacy variables

##### 4.1.3.1 Seizure-related other efficacy variables

For subjects from N01258 with generalized epilepsy:

- Generalized (type II) seizure days standardized to a 28-day duration by 3-month periods over the Evaluation Period
- Seizure days per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

Some variables may not be assessed if the number of subjects with generalized epilepsy is insufficient.

#### 4.1.3.2 Nonseizure-related other efficacy variables

The other efficacy variables are as follows:

- Medical resources use during the first 2 years of the Evaluation Period
- Change in QOLIE-31-P scores from the Baseline of N01358 or N01258 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in HADS scores from the Baseline of N01358 or N01258 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in socio-professional data from the Baseline of N01358 or N01258 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

#### 4.2 Safety variables

- AEs
- Laboratory tests (including hematology, blood chemistry, urinalysis, and pregnancy test, and additional endocrinology once a year )
- ECG
- Physical examination
- Neurological examination
- Vital signs
- Body weight

**Has been changed to:**

#### 4.1 Safety variables

##### 4.1.1 Primary safety variables

- Occurrence of a TEAE
- Withdrawal due to AE
- Occurrence of an SAE

##### 4.1.2 Other safety variables

- Laboratory tests (blood chemistry, hematology, urinalysis, endocrinology)

- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate) and body weight
- ECG
- Physical and neurological examinations
- Change in HADS scores from the Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

#### 4.2 Efficacy variables

##### 4.2.1 Secondary efficacy variables

For subjects with focal-onset epilepsy:

- POS (type 1) frequency per 28 days during the Evaluation Period
- Percent reduction in POS (type 1) frequency per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate in POS (type I) frequency over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period of the previous study.

No secondary efficacy variables are defined for subjects with generalized epilepsy.

##### 4.2.2 Other efficacy variables

For subjects with focal-onset epilepsy:

- Percentage of subjects continuously seizure free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period

For subjects with generalized epilepsy:

- Generalized (type II) seizure days per 28 days during the Evaluation Period
- Percent reduction in generalized (type II) seizure days per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate for generalized (type II) seizure days over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure days from the Baseline Period of the previous study.
- Percentage of subjects continuously seizure free for all seizure types (I+II+III) for at least 6 months and at least 12 months during the Evaluation Period

The following will be evaluated separately for subjects with focal-onset epilepsy and subjects with generalized epilepsy:

- Change in QOLIE-31-P scores from Baseline of the previous study to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

#### 4.3 Pharmacoeconomic variables

The following will be evaluated separately for subjects with focal-onset epilepsy and subjects with generalized epilepsy:

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and emergency room [ER] visits) during the first 2 years of the Evaluation Period
- Socio-professional data for each assessment for the first 2 years and for the last assessment during the first 2 years of the Evaluation Period

#### Change #7

### Section 5.2 Schedule of study assessments

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

The “Laboratory assessments” row was renamed “Laboratory safety assessments,” and this row now includes an ‘X’ for the MEV column. The corresponding ‘i’ footnote was added under the table and reads as follows:

<sup>i</sup> Liver function tests are the only laboratory assessments done at the MEV in M3 and M9 (see Section 10.5.1).

Subsequent footnotes were assigned sequential lettering due to the addition of new footnote.

A table row for C-SSRS was added and included this assessment at each study visit. In addition, the abbreviation C-SSRS and its definition were added to the table abbreviations.

#### Change #8

### Section 6.2 Exclusion criteria

The following exclusion criterion was added:

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.

#### Change #9

### Section 6.3 Withdrawal criteria

The following withdrawal criteria have been added to this section:

- Withdrawal criterion for subjects who completed a C-SSRS assessment at the Entry Visit:
  - Subject has active suicidal ideation as indicated by a positive response (“Yes”) to either Question 4 or 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.
- Withdrawal criteria for already enrolled subjects who did not complete a C-SSRS assessment at the Entry Visit:
  - Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the



“Already Enrolled Subjects” version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.

- Subject had active suicidal ideation prior to study entry or since study start as indicated by a positive response (“Yes”) to either Question 4 or Question 5 of the “Already Enrolled Subjects” version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
- Subject has active suicidal ideation as indicated by a positive response (“Yes”) to either Question 4 or 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 #10

#### Section 8 Study Procedures By Visit

The following C-SSRS assessment bullet was added to the lists for all study visits included in Section 8.1, Section 8.2, Section 8.3, Section 8.4, Section 8.6, and Section 8.8.

- **Suicidality assessment (C-SSRS)**

The laboratory safety assessment bullet in Section 8.1, Section 8.2, and Section 8.6 were updated as follows:

- Laboratory **safety** assessments: **hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)**

The laboratory safety assessment bullet in Section 8.4 was updated as follows:

- Laboratory **safety** assessments, including thyroid-stimulating hormone (TSH) assessments: **hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)**

The laboratory safety assessment bullet in Section 8.8 was updated as follows:

- 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)**

### Change #11

#### Section 8.5 Unscheduled Visit

The C-SSRS suicidality assessment has been added to the bulleted list for an Unscheduled Visit as follows:

- Suicidality assessment (C-SSRS)
  - If an Unscheduled Visit is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement

of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

#### **Change #12**

The title for Section 9.1 was changed.

#### **Original title:**

9.1 Additional efficacy assessments

#### **Has been changed to:**

9.1 Additional efficacy **and pharmacoeconomic** assessments

#### **Change #13**

The section describing the HADS scores assessment was moved from Section 9 Assessment of Efficacy to Section 10 Assessment of Safety to correspond with the realignment of variables in Section 4 Study Variables. No text in the section was changed, only the placement. After the deletion of the HADS scores section, the subsequent numbering of subsections within Section 9 changed accordingly.

#### **Original section:**

##### **Section 9.1.2 HADS scores**

The HADS (see Section 16.2) will be used to evaluate anxiety and depression/depressed mood of study subjects (Zigmond and Snaith, 1983). The HADS is an instrument that assesses the presence and severity of anxiety and depressed mood. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension (anxiety, depression) is calculated as recommended by the authors, ranging from 0 to 21 with higher scores indicating higher depression/anxiety. The HADS will be completed by subjects who are able to complete the assessments on their own, during the first 2 years at the FEV, YEV, Last Evaluation Period Visit, and EDV.

#### **Has been changed to:**

##### **Section 10.6.7 HADS scores**

The HADS (see Section 16.2) will be used to evaluate anxiety and depression/depressed mood of study subjects (Zigmond and Snaith, 1983). The HADS is an instrument that assesses the presence and severity of anxiety and depressed mood. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension (anxiety, depression) is calculated as recommended by the authors, ranging from 0 to 21 with higher scores indicating higher depression/anxiety. The HADS will be completed by subjects who are able to complete the assessments on their own, during the first 2 years at the FEV, YEV, Last Evaluation Period Visit, and EDV.

## Change #14

### Section 10.1.6 Pregnancy

#### Original text:

Paragraph 4:

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. The health of the child must be followed for 12 months after birth for any significant medical issues.

#### Has been changed to:

Any 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. The health of the child **may** be followed for 12 months after birth for any significant medical issues.

## Change #15

The following section was added to address the FDA Final Rule. The subsequent section numbering within Section 10 was changed accordingly.

### Section 10.4 Anticipated serious adverse events

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure: convulsion. This original list will remain in effect for the duration of the protocol.

The list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 10.2.2.

## Change #16

Due to the addition of Section 10.4 Anticipated serious adverse events, Section 10.4.1 Safety laboratory assessments was changed to Section 10.5.1 and the following change was made:

### Section 10.5.1 Safety laboratory assessments

#### Original text:

Under laboratory assessments table:

The creatinine clearance (Cr Cl) will be calculated by the Cockcroft's formula:

- Male:  $\text{Cr Cl mL/min} = [(140 - \text{age}) \times \text{body weight}] / [72 \times \text{serum creatinine (mg/day)}]$
- Female:  $\text{Cr Cl mL/min} = ([ (140 - \text{age}) \times \text{body weight}] / [72 \times \text{serum creatinine (mg/day)}]) \times 0.85$

#### Has been changed to:

The creatinine clearance (Cr Cl) will be calculated by the Cockcroft's formula:

- Male: Cr Cl mL/min=[(140-age) x body weight] / [72 x serum creatinine (mg/dL)]
- Female: Cr Cl mL/min=[(140-age) x body weight] / [72 x serum creatinine (mg/dL)] x 0.85

### **Change #17**

Due to the addition of Section 10.4 Anticipated serious adverse events, Section 10.5 Other safety measurements was changed to Section 10.6. The following subsection was added to this section:

#### **Section 10.6.6 Assessment of suicidality**

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures, Section 5.2.

### **Change #18**

## **Section 12 Statistics**

### **Original sections:**

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

#### **12.1 Definition of analysis populations**

Efficacy Populations will consist of all subjects who took at least 1 dose of study medication and have at least 1 seizure diary during the Evaluation Period. Separate Efficacy Populations will be defined for subjects with POS and subjects with generalized epilepsy.

The Safety Population will consist of all subjects who took at least 1 dose of study medication.

#### **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. Key supporting data will be provided in data listings. Summary statistics will be presented by the overall BRV dose.

#### **12.3 Planned efficacy analyses**

##### **12.3.1 Analysis of the primary efficacy variable**

The following primary efficacy variable will be summarized with descriptive statistics.

- The primary efficacy variable is the POS (type I) seizure frequency standardized to a 28-day duration. The primary efficacy variable will be summarized by 3-month periods over the Evaluation Period.

##### **12.3.2 Analysis of the secondary efficacy variables**

The following secondary efficacy variables will be summarized with descriptive statistics.

- Seizure frequency per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Responder rate in POS (type I) by 3-month periods over the Evaluation Period. A responder is defined as a subject with a  $\geq 50\%$  reduction in seizure frequency from the Baseline Period for the double-blind study N01358.

Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.

### **12.3.3 Analysis of the other efficacy variables**

#### **12.3.3.1 Seizure-related other efficacy variables**

For subjects from N01258 with generalized epilepsy:

- Generalized (type II) seizure days standardized to a 28-day duration by 3-month periods over the Evaluation Period
- Seizure days per 28 days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of seizure-free days for all seizure types (I+II+III) by 3-month periods over the Evaluation Period
- Proportion of continuously seizure-free subjects for all seizure types (I+II+III) by 3-month periods over the Evaluation Period

Some variables may not be assessed if the number of subjects with generalized epilepsy is insufficient.

#### **12.3.3.2 Nonseizure-related other efficacy variables**

The following other efficacy variables will be summarized with descriptive statistics.

- Medical resources use during the first 2 years of the Evaluation Period
- Change in QOLIE-31-P scores from the Baseline of N01358 or N01258 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in HADS scores from the Baseline of N01358 or N01258 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years
- Change in socio-professional data from the Baseline of N01358 or N01258 to each assessment for the first 2 years and to the last Evaluation Period assessment during the first 2 years

## 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 by time windows, by periods, and by categories of total duration of exposure.

All safety variables will be analyzed by descriptive methods on the Safety Population. Treatment-emergent adverse events will be summarized by categories of total duration of exposure, period, Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) Primary System Organ Class and Preferred Term in incidence tables. Separate tables will be provided, by categories of total duration of exposure, 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. ECG abnormalities, as well as physical and neurological abnormalities, will also be listed by period and visit.

### Has been changed to:

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

## 12.1 Definition of analysis populations

Efficacy Populations will consist of all subjects who took at least 1 dose of study medication and have at least 1 seizure diary **day** during the Evaluation Period. Separate Efficacy Populations will be defined for subjects **with focal epilepsy** and subjects with generalized epilepsy.

The Safety Population will consist of **all** subjects who took at least 1 dose of study medication.

## 12.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, median, 25th percentile, 75<sup>th</sup> percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Summary statistics will be presented **for all subjects combined**.

## 12.3 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 **for all subjects** and by categories of total duration of exposure.

All safety variables will be analyzed by descriptive methods on the Safety Population. Treatment-emergent adverse events will be summarized **in incidence tables** by categories of total duration of exposure **and by** Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) 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, as well as physical and neurological abnormalities, will also be listed by period and visit.

#### 12.4 Planned efficacy analyses

**All efficacy outcomes will be summarized with descriptive statistics only. Separate summaries will be provided for subjects with focal epilepsy and subjects with generalized epilepsy.**

**For subjects with focal epilepsy, 28-day adjusted seizure frequency will be calculated by dividing the number of partial seizures by the number of days for which the diary was completed, and multiplying the resulting value by 28. For subjects with generalized epilepsy, 28-day adjusted seizure days will be calculated by dividing the number of days with a generalized seizure by the number of days for which the diary was completed, and multiplying the resulting value by 28.**

**Responder rates will not be evaluated for subjects from N01258 due to the short duration of the Baseline Period for this study.**

**Some variables for subjects with generalized epilepsy may not be assessed if the number of subjects with generalized epilepsy is insufficient.**

**Change in QOLIE-31-P scores from Baseline of the previous study will be summarized with descriptive statistics for the first 2 years of the Evaluation Period.**

#### 12.5 Planned pharmacoeconomic analyses

**Direct cost parameters and socio-professional data will be summarized with descriptive statistics for the first 2 years of the Evaluation Period.**

### 16.5 Protocol Amendment 3

#### Rationale for the amendment

This protocol is being amended to align existing language with updated UCB Standard Operating Procedures (SOPs) and/or best practices as well as to allow for a named patient or compassionate use program (or similar) or for subjects to switch to another BRV study or to commercial BRV, if when, and where available.

#### Modifications and changes

##### Global changes

The following changes were made where applicable in this protocol:

- In accordance with new UCB SOP, the sponsor signature block was removed and replaced with a Sponsor Declaration ([Section 18](#)) and electronic signature.
- Outdated safety information was deleted from [Section 2.4](#)
- Update of the protocol contact information.



- The study duration language was revised to include the possibility of a named patient or compassionate use program (or similar) as a reason for ending the study duration.
- Language regarding Investigator deviation from the protocol in the event of a medical emergency ([Section 11.1](#)) was revised to align with current UCB standard language.

## Specific changes

### Change #1

Sponsor Declaration was moved from page 2 of protocol to [Section 18](#). Signature block was deleted due to use of electronic signature.

### Change #2

## STUDY CONTACT INFORMATION

### Original tables:

#### Clinical Project Manager

Name:	[REDACTED] MPH, MBA
Address:	8010 Arco Corporate Drive, Suite 100 Raleigh, NC 27617 United States
Phone:	[REDACTED]
Fax:	[REDACTED]

#### Clinical Trial Biostatistician

Name:	[REDACTED] MS
Address:	8010 Arco Corporate Drive, Suite 100 Raleigh, NC 27617 United States
Phone:	[REDACTED]
Fax:	[REDACTED]

#### Clinical Monitoring Contract Research Organization

Name:	PRA International
Address:	4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612 United States
Phone:	+1 919 786 8200
Fax:	+1 919 786 8201

## Have been changed to:

### Clinical Project Manager

Name:	[REDACTED], PhD
Address:	Alfred-Nobel-Str. 10 40789 Monheim am Rhein Germany
Phone:	[REDACTED]
Fax:	[REDACTED]

### Clinical Trial Biostatistician

Name:	[REDACTED], PhD
Address:	8010 Arco Corporate Drive, Suite 100 Raleigh, NC 27617 United States
Phone:	[REDACTED]
Fax:	[REDACTED]

### Clinical Monitoring Contract Research Organization

Name:	PRA HEALTHSCIENCES
Address:	4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612 United States
Phone:	+1 919 786 8200
Fax:	+1 919 786 8201

### Change #3

## SERIOUS ADVERSE EVENT REPORTING

Original table:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding		
<b>Fax</b>	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 21 <b>USA:</b> +1 800 880 6949 <b>Canada:</b> +1 877 582 8842 <b>Japan:</b> +81 3 5283 1869	
<b>Phone</b>	<b>During business hours:</b>	<b>Outside business hours:</b>
	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 68 <b>USA and Canada:</b> +1 404 895 0794 <b>Japan:</b> +81 3 5283 1814	<b>Europe and Rest of the World (except Japan):</b> +32 2 386 24 68 <b>USA and Canada:</b> +1 404 895 0794 <b>Japan:</b> +81 80 1100 5372

Has been changed to:

## SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
<b>Email</b>	<b>Global: DSICT@ucb.com</b>
<b>Fax</b>	<b>Europe and Rest of the World:</b> +32 2 386 2421 <b>USA:</b> +1 800 880 6949 <b>Canada:</b> +1 877 582 8842

## Change #4

### List of Abbreviations

The following abbreviation was deleted: GCSP Global Clinical Safety and Pharmacovigilance.

The following abbreviation was added: PS Patient Safety

## Change #5

### Section 1 Summary

#### Original text:

This study will enroll subjects ( $\geq 16$  years) from N01358 with refractory partial onset seizures (POS) whether or not secondarily generalized and subjects ( $\geq 16$  years) from N01258 with localization-related or generalized epilepsy. Subjects under 18 years may only be included where legally permitted and ethically accepted. Subjects have to complete the Treatment Period of N01358 or the Evaluation Period of N01258 prior to enrollment into N01379. Subjects from N01358 will be started on a BRV dose of 150mg/day 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 N01258 will start at a dose of BRV 200mg/day and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study. During the Evaluation Period, subjects will be invited to visit the clinical site monthly in the first 3 months and every 3 months thereafter. The completion of the Evaluation Period or early discontinuation from N01379 is followed by a Down-Titration Period of up to 4 weeks and by a subsequent Posttreatment Period (between 2 and 4 weeks) during which the subject does not receive study drug.

This LTFU study will run throughout the duration of the clinical development period of BRV, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults ( $\geq 16$  years) with refractory POS, whether or not secondarily generalized, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

#### Has been changed to:

This study will enroll subjects ( $\geq 16$  years) from N01358 with refractory partial onset seizures (POS) whether or not secondarily generalized and subjects ( $\geq 16$  years) from N01258 with localization-related or generalized epilepsy. Subjects under 18 years may only be included where legally permitted and ethically accepted. Subjects have to complete the Treatment Period of N01358 or the Evaluation Period of N01258 prior to enrollment into N01379. Subjects from N01358 will be started on a BRV dose of 150mg/day 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 N01258 will start at a dose of BRV 200mg/day and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment.

The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study. During the Evaluation Period, subjects will be invited to visit the clinical site monthly in the first 3 months and every 3 months thereafter. The completion of the Evaluation Period or early discontinuation from N01379 is followed by a Down-Titration Period of up to 4 weeks and by a subsequent Posttreatment Period (between 2 and 4 weeks) during which the subject does not receive study drug, **or subjects will be converted without down-titration to commercial BRV if, when, and where available. Alternatively, subjects may transition into another BRV study, or be initiated without down-titration into a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific legal and regulatory requirements.**

This LTFU study will run throughout the duration of the clinical development period of BRV, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults ( $\geq 16$  years) with refractory POS, whether or not secondarily generalized; until the Sponsor decides to close the study; **until subjects transition to another BRV study; until a managed access program, named patient program, compassionate use program, or similar type of access program is established as allowed per country-specific requirement in addition to legal and regulatory guidelines;** or until BRV development is stopped by the Sponsor.

## Change #6

### Section 2.4 Safety of BRV

#### Original text:

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

In addition, there are 2 ongoing open-label LTFU studies (N01125 and N01199) that include subjects with POS who completed one of the above Phase 2/3 well-controlled studies. As of 05 Jan 2010, 1521 subjects have been enrolled into these studies and 1516 received study medication. The median duration of BRV exposure in LTFU studies was 52 weeks. The most frequently reported TEAEs based on interim safety monitoring review include headache, dizziness, nasopharyngitis, somnolence, convulsion, and fatigue. The most frequent TEAEs leading to premature discontinuation were convulsion, pregnancy, and depression. The only SAE occurring at a frequency  $>1\%$  was convulsion (1.8%).

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

#### Has been changed to:

In Phase 2/3 studies, a favorable safety and tolerability profile has been demonstrated for BRV. The discontinuation rate and the discontinuation rate due to treatment-emergent

adverse events (TEAEs) were low for all studies. The most frequently reported TEAEs were headache, somnolence, dizziness, and fatigue. The overall incidence of serious adverse events (SAEs) was low. There were no clinically relevant changes in laboratory values, vital signs, or ECG abnormalities.

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

## Change #7

### Section 5.1 Study description

#### Original text:

This is a Phase 3, open-label, LTFU, multicenter, noncomparative, and single-arm study. The subject population will be adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized from N01358 and subjects with localization-related or generalized epilepsy from N01258. Subjects under 18 years may be included only where legally permitted and ethically accepted. Subjects must complete the Treatment Period of N01358 or the Evaluation Period of N01258 prior to enrollment into N01379. Upon completion or early discontinuation from N01379, there will be a Down-Titration Period, followed by a Posttreatment Period during which the subject will not receive study drug.

This LTFU study will run throughout the duration of the clinical development period of BRV, and will continue until a marketing authorization is granted by any Health Authority in an indication for the adjunctive treatment in adults ( $\geq 16$  years) with refractory POS, whether or not secondarily generalized, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

Subjects from N01358 will be started on oral BRV at a dose of 150mg/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 N01258 will be started at an oral dose of BRV 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study and must always be administered as a symmetrical morning and evening dose.

#### Has been changed to:

This is a Phase 3, open-label, LTFU, multicenter, noncomparative, and single-arm study. The subject population will be adults ( $\geq 16$  years) with refractory POS whether or not secondarily generalized from N01358 and subjects with localization-related or generalized epilepsy from N01258. Subjects under 18 years may be included only where legally permitted and ethically accepted. Subjects must complete the Treatment Period of N01358 or the Evaluation Period of N01258 prior to enrollment into N01379. Upon completion of the Evaluation Period or early discontinuation from N01379 there will be a Down-Titration Period followed by a Posttreatment Period during which the subject does not receive study drug, **or subjects will be converted without down-titration to commercial BRV if, when, and where available. Alternatively, subjects may transition into another BRV study, or be initiated without**



**down-titration into a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific legal and regulatory requirements.**

Subjects from N01358 will be started on oral BRV at a dose of 150mg/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 N01258 will be started at an oral dose of BRV 200mg/day (2 equally divided doses administered twice daily) and should be maintained at this dose for at least 2 weeks unless the subject is unable to tolerate treatment. The BRV dose can be adjusted based on the individual subject's seizure control and tolerability. However, the BRV dose may not exceed 200mg/day during the study and must always be administered as a symmetrical morning and evening dose.

## **Change #8**

### **Section 5.1.1 Study duration per subject**

#### **Original text:**

Subject recruitment for the study will begin in approximately Q2 2011. For each subject, the study will last from study entry until either regulatory approval of BRV has been granted by any Health Authority in an indication of adjunctive treatment of POS, until the Sponsor decides to close the study, or until BRV development is stopped by the Sponsor.

The following study periods are defined:

- Evaluation Period (Visit 1 until the Last Evaluation Period Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in N01379 will immediately 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 20mg/day for 1 week should be included prior to the Posttreatment Period.
- Posttreatment Period (2 to 4 weeks): 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 Posttreatment Period for a minimum of 2 weeks and a maximum of 4 weeks, followed by a Final Visit (FV).
- The end of the study is defined as the date of the last visit of the last subject in the study.

#### **Has been changed to:**

Subject recruitment for the study will begin in approximately Q2 2011. For each subject, the study will last from study entry until either regulatory approval of BRV has been granted by any Health Authority in an indication of adjunctive treatment of POS, until the Sponsor decides to close the study; **until subjects transition to another BRV study; until a managed access program, named patient program, compassionate use program, or**



**similar type of access program is established as allowed per country-specific requirement in addition to legal and regulatory guidelines;** or until BRV development is stopped by the Sponsor.

The following study periods are defined:

- Evaluation Period (Visit 1 until the Last Evaluation Period Visit or Early Discontinuation Visit [EDV]): Subjects who enroll in N01379 will immediately 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 20mg/day for 1 week should be included prior to the Posttreatment Period.
- Posttreatment Period (2 to 4 weeks): 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 Posttreatment Period for a minimum of 2 weeks and a maximum of 4 weeks, followed by a Final Visit (FV).
- The end of the study is defined as the date of the last visit of the last subject in the study.

**For subjects who transition to another BRV study or a managed access program or similar type of program or who will be converted to commercial BRV if, when, and where available, the Down-Titration Period and FV are not applicable.**

## Change #9

**Table 5-1: Schedule of study assessments**

**Original table:**

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV])	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	V1	V3, V5, V9...	V2, V4, V6, V8, V10...	V7...	NA	NA	NA	5.3
<b>Month</b>	M0	M2, M6, M18...	M1, M3, M9, M15, M21...	M12...	NA	NA	NA	5.3
<b>ASSESSMENTS</b>								
End of study status <sup>m</sup>							X	8.8

<sup>m</sup> End of study status will be completed at the FV for subjects having performed an EDV (discontinued subjects) and for subjects leaving the study at the end of the program (completed subjects).

**Has been changed to:**

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Last Evaluation Period Visit (or Early Discontinuation Visit [EDV])	Down-Titration Phone Call (DTP) <sup>a</sup>	Final Visit (FV)	Reference to Section
<b>Visit</b>	V1	V3, V5, V9...	V2, V4, V6, V8, V10...	V7...	NA	NA	NA	<b>5.3</b>
<b>Month</b>	M0	M2, M6, M18...	M1, M3, M9, M15, M21...	M12...	NA	NA	NA	<b>5.3</b>
<b>ASSESSMENTS</b>								
End of study status <sup>m</sup>					X		X	<b>8.8</b>

<sup>m</sup> 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 may transition into another BRV study, or be initiated without down-titration in a managed access program, named patient program, compassionate use program, or similar type of access program as allowed per country-specific legal and regulatory requirements, or for subjects who will be converted without down-titration to commercial BRV if, when, and where available.

## Change #10

### Section 8.6 Last Evaluation Period Visit or Early Discontinuation Visit

#### Original text:

- QOLIE-31-P (if the EDV occurs within the first 2 years)
- HADS (if the EDV occurs within the first 2 years)
- Vital signs
- Weight
- Physical examination
- Neurological examination
- ECG
- IVRS call
- DRC dispensed
- DRC retrieved
- Recording of seizures
- Hospital stays (if the EDV occurs within the first 2 years)
- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol (if the EDV occurs within the first 2 years)
- Socio-professional data (if the EDV occurs within the first 2 years)
- Laboratory safety assessments: hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing
- Drug return/accountability

#### Has been changed to:

**For subjects who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available), the EDV will need to be completed; however, down-titration and FV are not applicable.**

- QOLIE-31-P (if the EDV occurs within the first 2 years)
- HADS (if the EDV occurs within the first 2 years)
- Vital signs
- Weight
- Physical examination
- Neurological examination
- ECG
- IVRS call
- DRC dispensed (**if applicable; DRC not dispensed if subject will not down-titrate**)
- DRC retrieved
- Recording of seizures
- Hospital stays (if the EDV occurs within the first 2 years)
- Suicidality assessment (C-SSRS)
- Healthcare provider consultations not foreseen by the protocol (if the EDV occurs within the first 2 years)
- Socio-professional data (if the EDV occurs within the first 2 years)
- Laboratory safety assessments: hematology, blood chemistry, urinalysis, and urine pregnancy test (if applicable)
- Recording of AEs
- Medical procedures
- Concomitant AED
- Concomitant non-AED
- Drug dispensing (**if applicable; drug not dispensed if subject will not down-titrate**)
- Drug return/accountability
- **End of study status (if the subject will not down-titrate)**

## Change #11

### Section 8.7 Down-Titration Phone Call

#### Original text:

- Recording of AEs

The Down-Titration Phone Call at the end of the Down-Titration Period is mandatory.

### **Has been changed to:**

- Recording of AEs

The Down-Titration Phone Call at the end of the Down-Titration Period is mandatory.

**Down-titration is not applicable to subjects who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available).**

### **Change #12**

#### **Section 8.8 Final Visit**

The following text was added after the list of Final Visit procedures:

**The FV is not applicable to subjects who transition to another BRV study or a managed access program or similar type of program or who convert to commercial BRV (if, when, and where available).**

### **Change #13**

#### **Section 10.1.6 Pregnancy**

##### **Original text:**

Should a subject become pregnant after the first intake of any IMP, UCB's Global Clinical Safety and Pharmacovigilance (GCSP) department should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known and the following should be completed:

##### **Has been changed to:**

Should a subject become pregnant after the first intake of any IMP, UCB's **Patient Safety (PS)** department should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known and the following should be completed:

### **Change #14**

#### **Section 10.2.2 Procedures for reporting serious adverse events**

##### **Original text:**

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact numbers 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 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.

##### **Has been changed to:**

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact **details** 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 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.

## **Change #15**

### **Section 10.2.3 Follow-up of serious adverse events**

#### **Original text:**

An SAE 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.

Information on SAEs obtained after clinical database lock will be captured through the GCSP database without limitation of time.

#### **Has been changed to:**

An SAE 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.

Information on SAEs obtained after clinical database lock will be captured through the **PS** database without limitation of time.

## **Change #16**

### **Section 11.1 Adherence to protocol**

#### **Original text:**

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken. 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 appropriate regulatory authorities, if applicable, prior to being implemented.

#### **Has been changed to:**

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 of the sponsor within 24 hours and follow any local regulatory requirements.** 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 appropriate regulatory authorities, if applicable, prior to being implemented.



## 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 sub-Investigators 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:

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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.

REDACTED COPY

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

## N01379 Protocol amendment 3

### ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
	Clinical Approval	19-May-2015 16:16 GMT+0
	Clinical Approval	19-May-2015 16:16 GMT+0