1. TITLE

Protocol of Study N01315

An open-label, multinational, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam, used at a flexible dose up to a maximum of 200mg/day, in subjects aged 16 years or older suffering from epilepsy.

Sponsor:
UCB Biosciences, Inc
8010 Arco Corporate Drive
Raleigh, NC 27617
UNITED STATES

Hereafter "UCB"

Brivaracetam - EudraCT Number: 2008-001433-98; IND Number: 70,205

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Principal Investigator

By my signature below, I acknowledge that I have read the protocol (RPCE08C0502) and agree that it contains all necessary details for carrying out the clinical study described therein. Furthermore, I agree to conduct this clinical study in compliance with said Protocol, the ICH Good Clinical Practice guideline, as well as with any and all applicable federal, state and/or local laws and regulations and with my contractual obligations towards UCB or its representatives(s).

Signature: _____ Date: _____

Printed Name: _____

Address: _____

_____

Phone: _____ Site Number: _____

2. CONTACT INFORMATION

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Investigator(s)
The complete and updated list of Investigators is maintained in the Trial Master File (TMF) at UCB.

Signatory Coordinating Investigator(s)
The signatory coordinating Investigator will be designated by UCB.

3. TABLE OF CONTENTS

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4. LIST OF ABBREVIATIONS

AE	Adverse event
AED(s)	Antiepileptic Drug(s)
ALT(ALAT/SGPT)	Alanine Aminotransferase
AST (ASAT/SGOT)	Aspartate Aminotransferase
b.i.d.	Twice daily
BRV	brivaracetam
CNS	Central Nervous System
CPM	Clinical Project Manager
Cr Cl	Creatinine Clearance
CRF	Case Report Form
CRO	Clinical Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTM	Clinical Trial Manager
CTS	Clinical Trials Supplies
CV	Curriculum Vitae
CYP	Cytochrome P450
DRC	Daily Record Card
ECG	Electrocardiogram
EDV	Early Discontinuation Visit
EEG	Electroencephalogram
EQ-5D	EuroQoL-5 Dimensions
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LTFU	Long-term Follow-up
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PBO	Placebo
PK	Pharmacokinetic(s)

POS	Partial onset seizure(s)
PRO	Patient Reported Outcome
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Questionnaire
RBC	Red Blood Cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV2A	Synaptic vesicle protein 2A
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
V	Visit
WBC	White Blood Cell

5. PROTOCOL SUMMARY

TITLE OF THE STUDY
An open-label, multinational, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam used at a flexible dose up to a maximum of 200mg/day in subjects aged 16 years or older suffering from epilepsy.

STUDY TYPE/PHASE
Phase III

STUDY OBJECTIVES

Primary Objective
To evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses with a maximum of 200mg/day in subjects suffering from epilepsy.

Secondary Objective
To evaluate the maintenance of efficacy over time of BRV.

Exploratory Objectives
- To explore impact on health-related quality of life, anxiety and depression.
- To obtain a description of patient's self-reported health status.
- To collect data on medical resources used and on indirect cost parameters.

STUDY VARIABLES

Primary Safety Variables

- Occurrence of a treatment-emergent adverse event (TEAE)
- Withdrawal due to AE
- Occurrence of a serious adverse event (SAE)

Other Safety Variables

- Laboratory tests (blood chemistry, hematology, and urinalysis)
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate) and body weight
- Electrocardiogram (ECG)
- Physical and neurological examination

- Change in Hospital Anxiety and Depression Scale (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

Secondary Efficacy Variables

- Percentage of subjects on continuous BRV monotherapy for at least 3 months, at least 6 months, and at least 12 months of the Evaluation Period

Other Efficacy Variables

- Partial onset seizure (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
- 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
- Change in Patient Weighted Quality of Life in Epilepsy Questionnaire (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
- EuroQoL-5 Dimensions (EQ-5D) questionnaire response for each assessment for the first 2 years for the Evaluation Period and for the last assessment during the first 2 years of the Evaluation Period

Pharmacoeconomic Variables

- 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
- Indirect costs (workdays or schooldays lost by the subject and days subject received help from a caregiver) 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

Pharmacokinetic Variables

- Brivaracetam (parent compound only) plasma levels
- Concomitant antiepileptic drugs (AEDs) (and/or relevant metabolites) plasma levels

STUDY DESIGN

This is a Phase III, long-term follow-up (LTFU), multinational, multicenter, non-comparative, open-label and single arm study.

The visits will be scheduled as follows:

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

PLANNED STUDY PERIOD
This 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 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 requirements in addition to legal and regulatory guidelines, or until BRV development is stopped by the Sponsor.

PLANNED NUMBER OF SUBJECTS AND SITES:
It was estimated that approximately 300-600 subjects were to enter the study. However, the number of subjects entered will be reduced due to the premature discontinuation of N01276 and N01306.

This study will include as many sites as required (initially, 120-180 sites are foreseen).

REGIONS AND COUNTRIES
The study is planned to be performed worldwide.

MAIN INCLUSION AND EXCLUSION CRITERIA
Before any study procedures are initiated for any subject in this study, an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved written informed consent form will be properly executed and documented.

Subject Inclusion Criteria:
- An IEC/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.

- Male/female subjects from 16 years or older. Subjects under 18 years may only be included where legally permitted and ethically accepted. In [redacted] all subjects must be older than 18 years.
- Subjects with epilepsy who participated in previous BRV studies which allow access to the present study.
- Subjects from whom the Investigator believes a reasonable potential benefit from the long-term administration of BRV may be expected.
- Female subjects without childbearing potential (premenarcheal; 2 years postmenopausal, bilateral oophorectomy or ovariectomy, bilateral salpingectomy, complete hysterectomy, congenital sterility) are eligible. Female subjects with childbearing potential are eligible if they use a medically accepted contraceptive method for the duration of the study (Intra Uterine Device, diaphragm with spermicide, male or female condom with spermicide; oral hormonal contraceptive, non-oral hormonal contraceptive medication, bilateral tubal ligation, bilateral tubal implant, monogamous relationship with vasectomized partner). Oral or depot contraceptive treatment with at least 30µg [or 50µg if associated with other antiepileptic drugs known as inducers] ethinylestradiol per intake must be used in conjunction with a barrier method. 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. Sexual inactivity might be accepted on a case-by-case basis.
- Subject/legally acceptable representative considered as reliable and capable of adhering to the protocol (e.g. able to understand and complete diaries and questionnaires), visit schedule or medication intake according to the judgment of the Investigator.

Subject Exclusion Criteria:

- Severe medical, neurological and psychiatric disorders, including current suicidal ideation or behaviour, or laboratory values which may have an impact on the safety of the subject, as determined by the Investigator.
- Poor compliance with the visit schedule or medication intake in the previous BRV study.
- Participation in any clinical study of another investigation drug or device during the study.
- Pregnant or lactating woman.

INVESTIGATIONAL PRODUCT

Oral tablets of 10mg and 25mg BRV, packaged in bottles containing 200 oral tablets.

Subjects will begin at a recommended dose of BRV 100mg/day. The daily dose should be divided into 2 equal intakes (morning and evening), taken with or without food. The first intake will be in the evening of the day of the dispensation of the study medication. Subjects will continue BRV treatment at a dose up to a maximum of 200mg/day in twice daily (b.i.d.) administration. Up- and down-titration steps should be performed in steps of

maximum 50mg/day on a weekly basis. Full down-titration should include a 1-week step on 20mg/day.

The doses administered in this study must comply with doses that can be administered with either BRV 10mg tablets, 25mg tablets, or a combination of these 2 strengths in a total daily dose that can be administered in 2 equal doses. Daily dose prescriptions that do not respect these limitations should not be administered.

Each subject will be informed on how to take the drug and that there might be an excess of drug dispensed at each visit.

STATISTICAL METHODS

Population for Analysis

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

The Efficacy Population 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.

Safety Variables Analyses

All safety analyses will be summarized descriptively. Changes from Baseline will be calculated from the Baseline of the preceding study.

Efficacy Variables Analyses

No hypothesis testing will be performed.

All efficacy analyses will be summarized descriptively. The Baseline of an efficacy variable will be the Baseline from the initial study.

Sample Size Calculation

For this open-label, LTFU study, no sample size calculation has been performed. The sample size will depend upon recruitment into and completion of preceding studies; approximately 300 - 600 subjects were expected.

5.1 Study Schedule of Assessments

Table 5:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)[l]	Down-Titration Phone Call (DTP)[a]	Final Visit (FV)	Reference to Section
ASSESSMENTS									
Written Informed Consent	X								11.1.1
Clinical Study Subject Card Dispensing	X								11.1.2
Verification Inclusion/ Exclusion Criteria	X								11.1.3
Demographic Data	X								11.1.4
Childbearing Potential	X								11.1.5
Medical and Procedures History	X[b]								11.1.6
Epilepsy History	X[b]								11.1.7
AED History	X[b]								11.1.8
Vital Signs	X[c]	X	X	X	X	X		X	11.1.9
Weight and Height[d]	X[c]	X		X		X		X	11.1.10
Physical Examination	X[c]	X		X		X		X	11.1.11
Neurological Examination	X[c]	X		X		X		X	11.1.12
ECG[e]	X[c]			X		X		X	11.1.13
Daily Record Card Dispensed	X[c]	X	X	X		X			11.1.14
Daily Record Card Retrieval		X	X	X		X		X	11.1.14
Seizure Counts	X	X	X	X		X		X	11.1.14
Recording of Seizures	X[c]	X	X	X		X		X	11.1.14
QOLIE-31-P[f]		X		X		X			11.1.20.1
HADS[f]		X		X		X			11.1.20.2
EQ-5D[f]		X		X		X			11.1.20.3

Table 5:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)[l]	Down-Titration Phone Call (DTP)[a]	Final Visit (FV)	Reference to Section
ASSESSMENTS									
Workdays and schooldays lost / Days with caregiver's help [k]		X	X	X	X	X		X	
Hospital stay [k]		X	X	X	X	X		X	11.1.21
Healthcare Provider Consultations not foreseen by the protocol [k]		X	X	X	X	X		X	11.1.22
Socio-professional data[g]				X		X		X	11.1.23
Laboratory Assessments[h]	X[c]	X		X		X		X	11.1.15
Recording of Adverse Events	X	X	X	X	X	X	X	X	11.1.16
C-SSRS[j]		X	X	X	X	X		X	11.1.17
Medical Procedures	X	X	X	X	X	X		X	11.1.6
Concomitant AED	X	X	X	X	X	X		X	11.1.19
Concomitant Non-AED	X	X	X	X	X	X		X	11.1.19
Drug Dispensing	X	X	X	X		X			
Drug Return/Accountability		X	X	X		X		X	
End of Study Status[i]								X	11.1.24

AED=antiepileptic drug; AV=Additional Visit; BRV=brivaracetam; CRF=Case Report Form; C-SSRS=Columbia Suicide Severity Rating Scale; DTP=Down-Titration Phone Call; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EQ-5D=EuroQoL-5 Dimensions; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; HADS=Hospital Anxiety and Depression Scale; IEC=Independent Ethics Committee; IRB=Institutional Review Board; MEV=Minimal Evaluation Visit; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Questionnaire; YEV=Yearly Evaluation Visit

[a] Down-Titration Phone Call at the end of the Down-Titration Period is mandatory in case the subjects discontinue from more than 20mg/day BRV.
[b] The following data will be obtained from the database of the Baseline Visit of the previous study and should not be recorded into the CRF: General Medical and Procedure History, AED History, and Epilepsy History.
[c]) The following data will be obtained from the database of the final visit of the previous study and should not be recorded in the CRF: Vital Signs, Weight, Physical Examination, Neurological Examination, ECG, Recording of seizures, Laboratory Assessment including Safety (blood chemistry, hematology, and urinalysis), concomitant AED plasma levels and BRV plasma levels.
[d] Height will be recorded at Visit 1. Height will also be measured at each YEV and the FV for those subjects who are still potentially growing.

Table 5:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)[l]	Down-Titration Phone Call (DTP)[a]	Final Visit (FV)	Reference to Section
ASSESSMENTS									

[e] At FV, ECG is mandatory except if FV follows an EDV-where ECG results were normal.
[f] QOLIE-31-P, EQ-5D, and HADS are to be completed at the beginning of the visit by all subjects who are not mentally impaired during the first 2 years.
[g] Socio-professional data (to be collected during the first 2 years) will not be collected in [redacted]
[h] Laboratory assessment includes blood chemistry, hematology, and urinalysis; where applicable (women of childbearing potential), a serum pregnancy test will be done. Laboratory is mandatory at FV except if FV follows an EDV where laboratory results were normal. Concomitant AED plasma levels and BRV plasma levels up to approval of Protocol Amendment 2.
[i] 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).
[j] The C-SSRS assessment will be implemented by site per IRB/IEC approval upon completion of required training. As of the time of Protocol Amendment 2, all subjects had completed their EV. Thus, the C-SSRS was not assessed for any subjects at their EV.
[k] Procedures only performed during the first 2 years of subject participation in the study or EDV/FV in case the subject discontinues participation within the first 2 years.
[l] For subjects that may transition to another BRV study or a managed access program or similar type of program, the EDV will need to be completed, however down- titration and FV may not be applicable.

5.2 Schematic Diagram

- First year:
  - First 3 months: 1 visit/month: FEV alternating with MEV
  - Next 9 months: 1 visit/3 months: FEV alternating with MEV
- Second and subsequent years:
  - 1 visit/3months: FEV alternating with MEV
  - The YEV will be performed in replacement of the first FEV of each year.

Table 5:2 Visit Schematic Diagram

1st, 2nd and subsequent years follow-up		
Month	**Visit**	**Type of Visit**
M0	V1	Entry Visit (EV)
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV
M4		
M5		
M6	V5	FEV
M7		
M8		
M9	V6	MEV
M10		
M11		
M12	V7	YEV
M15	V8	MEV
M18	V9	FEV
M21	V10	MEV
M24	V11	YEV
M…	V…	…

In case the subject will not continue with the study drug, the Investigator will first plan an Early Discontinuation Visit (EDV) followed by the progressive down-titration of the study drug. 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 drug free period.

At the end of the down-titration period, a phone call will be given to subjects having down-titrated from doses higher than 20mg/day. The down-titration period will be followed by a period free of study drug of a minimum of 2 weeks and a maximum of 4 weeks and subsequently, the Final Visit (FV) will occur.

When the time point is reached at which the study will be terminated by the Sponsor (as defined in Section 8.4), subjects will discontinue the study drug, following the Investigator's instructions for down-titration if necessary.

6. BACKGROUND INFORMATION

6.1 Background and epidemiology of targeted disease

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

Diagnosis of epilepsy is based on the recurrence of seizures. Seizures may be caused by an underlying brain disorder or lesion or due to genetic conditions. Characterization of the epileptic syndrome has profound implications for treatment and prognosis. The major dichotomy for the diagnosis of epilepsy is the differentiation between focal epilepsies (i.e., 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 International League Against Epilepsy ([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 (EEGs) 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).

6.2 Background information regarding product

Brivaracetam is a 2-pyrrolidone derivative. Brivaracetam displays a high and selective interaction with a novel brain-specific binding site, SV2A (synaptic vesicle protein 2A). This binding site appears to be the major target for its pharmacological activity. Brivaracetam 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) are dose-proportional (at least from 10mg to 600mg). Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5L/kg, a value that is close to that of total body water. The plasma half-life of BRV is approximately 8 hours in young healthy male adults. The main metabolic pathway of BRV is by hydrolysis of the acetamide group to the corresponding carboxylic acid, while a second pathway is the ω1-hydroxylation mediated by cytochrome P450 2C19 (CYP2C19) (with contributions of several other isoenzymes). The combination of these 2 pathways results in the hydroxyacid terminal metabolite. These metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, with less than 9% as unchanged BRV, is excreted in urine within 72 hours after dosing.

Pharmacokinetic studies in elderly 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 30µg and levonorgestrel 150µg. 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, levetiracetam, oxcarbazepine metabolite, phenobarbital, phenytoin, topiramate, valproate, and zonisamide. Carbamazepine epoxide was moderately increased from Baseline at all BRV doses greater than 20mg/day, nearly reaching the upper limit of normal (3.0µg/mL) at BRV doses of 100 and 150mg/day.

6.3 Efficacy with BRV in fixed-dose Phase II/III studies in POS

Following completion of the Phase II studies (N01114, UCB protocol reference code RPCE02K0301; N01193, UCB protocol reference code RPCE05C2201), clinical results supported further development of BRV for the adjunctive treatment of POS. Two adequate and well-controlled fixed-dose studies (N01252, UCB protocol reference code RPCE06G0704; N01253, UCB protocol reference code RPCE06G0705) 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 the primary efficacy endpoint (for BRV 50mg/day) of N01252 was not positive, it provided supporting evidence for the efficacy of BRV 100mg/day in subjects with epilepsy. An additional confirmatory study (N01358) in subjects with POS is ongoing and will assess the doses of BRV 100mg/day, to replicate and confirm the treatment effect observed in N01252, and BRV 200mg/day, at the recommendation of regulatory authorities in order to explore the upper end of the dose-response curve.

6.4 Conversion to monotherapy

Two Phase III studies (N01276 and N01306) were initiated to evaluate the efficacy, safety and tolerability of BRV (at doses of 50 and 100mg/day in b.i.d. regimen) in the conversion to monotherapy, in subjects with POS, whether or not secondarily generalized, when compared to a historical pseudo-placebo control group.

A decision was taken to stop the N01276 and N01306 studies after an interim analysis and independent unblinded review of study data by a Data Monitoring Committee identified that pre-defined criteria for stopping the studies had been met. It was determined the probability that both studies together would demonstrate a positive outcome for the efficacy analysis at completion was too low.

6.5 Safety with BRV

In Phase II/III studies, a favorable safety and tolerability profile has been demonstrated for BRV. The discontinuation rate and the discontinuation rate due to TEAEs were low and similar to placebo (PBO) for all studies. The most frequently reported TEAEs were headache, somnolence, dizziness, and fatigue. The overall incidence of SAEs was low and similar to PBO. 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 (UCB reference code RXCE06E2216).

6.6 Study Rationale

The Sponsor wishes to develop BRV as a monotherapy antiepileptic treatment in subjects 16 years and older suffering from epilepsy. N01315 will give subjects, who have participated in a previous BRV monotherapy study in epilepsy, the opportunity to continue BRV treatment under the present protocol.

The study will explore the long-term safety and efficacy of BRV in such a population and potentially populations from other future studies.

6.6.1 Dose Selection

In this study, the recommended starting dose is 100mg/day. Afterwards the daily dose can be individualized up to a maximum of 200mg/day. Twice daily dosing is deemed necessary to ensure more regular exposure over the 24-hour interval.

A maximum dose of 200mg/day was chosen following consultation with regulatory authorities and is to be evaluated in more recent BRV studies (e.g., N01358 and N01379). According to available data, 200mg/day doses have been well tolerated.

6.6.2 Subject Population

Male and female subjects, with a clinical diagnosis of epilepsy with POS, are allowed to participate in this study from the age of 16 (where legally permitted and ethically accepted).

Indeed epilepsy features in the range of 16 to 18 years do not differ from the ones of older subjects, and efficacy of the AEDs seems to be comparable (N01236; CPMP/EWP/566/98 rev 1, 2000). In [redacted] however the minimal age to enter the study will be 18.

Depending on country-specific regulations, those subjects may be considered as adolescents or adults (N01125; CPMP/ICH/2711/99, 2000). In case they are considered as adolescents, parent(s) or legal representative will sign the informed consent form. The consent form or a specific assent form, where required, will be signed and dated by the minor.

6.6.3 Treatment Duration

The study is planned to begin in Q3 2008.

This 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 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.

6.6.4 Statement

The present study will be conducted in accordance with:

- This protocol.
- Code of Federal Regulations Title 21 Parts, 50, 54, 56, 312, and 314.
- International Conference on Harmonization: ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
- The principles that have their origin in the Declaration of Helsinki.
- All applicable laws and regulations.

7. STUDY OBJECTIVES

7.1 Primary Objective

To evaluate the long-term safety and tolerability of BRV at individualized doses with a maximum of 200mg/day in subjects suffering from epilepsy.

7.2 Secondary Objective

To evaluate the maintenance of efficacy over time of BRV.

7.3 Exploratory Objectives

- To explore impact on health-related quality of life, anxiety and depression.
- To obtain a description of patient's self-reported health status.
- To collect data on medical resources used and on indirect cost parameters.

8. STUDY DESIGN

8.1 Type/Design

This is a Phase III, LTFU, multinational, multicenter, non-comparative, open-label and single arm study.

The visits will be scheduled as follows:

- First year:
  - First 3 months: 1 visit/month: FEV alternating with MEV.
  - Next 9 months: 1 visit/3 months: FEV alternating with MEV.
- Second and subsequent years:
  - 1 visit/3months: FEV alternating with MEV.
  - The YEV will be performed in replacement of the first FEV of each year.

8.2 Subjects/Sites Numbers

It was estimated that approximately 300 - 600 subjects were to enter the study. However, the number of subjects entered will be reduced due to the premature discontinuation of N01276 and N01306.

This study will include as many sites as required (initially, 120-180 sites are foreseen).

8.3 Measures to Minimize/Avoid Bias

8.3.1 Blinding

This is a single arm open-label LTFU study.

8.3.2 Randomization

Not applicable.

8.3.3 Subject Identifier

Each subject will be identified by initials (3 letters; corresponding either to the subject's actual initials, or "dummy" initials, as preferred by the Investigator and according to country regulatory requirements) and a unique identifier including the study number, a 3-digit center number and a 4-digit sequential number, starting by 1 at each site (e.g. 1st subject at site 025: N01315/025/0001).

8.4 Study Duration

This 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 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.

8.5 End of Study

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

9. SELECTION AND WITHDRAWAL OF SUBJECTS

Before any study procedures are initiated for any subject in this study, an Independent Ethics Committee/Institutional Review Board (IEC/IRB) approved written informed consent form will be properly executed and documented.

9.1 Subject Inclusion Criteria

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

- An IEC/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.
- Male/female subjects from 16 years or older. Subjects under 18 years may only be included where legally permitted and ethically accepted. In [redacted] subjects must be older than 18 to enter the study.
- Subjects with epilepsy who participated in previous BRV studies which allow access to the present study.
- Subjects from whom the Investigator believes a reasonable potential benefit from the long-term administration of BRV may be expected.
- Female subjects without childbearing potential (premenarcheal; 2 years postmenopausal bilateral oophorectomy or ovariectomy, bilateral salpingectomy, complete hysterectomy, congenital sterility) are eligible. Female subjects with childbearing potential are eligible if they use a medically accepted contraceptive method for the duration of the study (Intra Uterine Device, diaphragm with spermicide, male or female condom with spermicide; oral hormonal contraceptive, non-oral hormonal contraceptive medication, bilateral tubal ligation, bilateral tubal implant, monogamous relationship with vasectomized partner). Oral or depot contraceptive treatment with at least 30µg [or 50µg if associated with other antiepileptic drugs known as inducers] ethinylestradiol per intake must be used in conjunction with a barrier method. 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. Sexual inactivity might be accepted on a case-by-case basis
- Subject/legally acceptable representative considered as reliable and capable of adhering to the protocol (e.g. able to understand and complete diaries and questionnaires), visit schedule or medication intake according to the judgment of the Investigator.

9.2 Subject Exclusion Criteria

Subjects must be excluded if they meet any of the following criteria:

- Severe medical, neurological and psychiatric disorders, including current suicidal ideation or behaviour, or laboratory values which may have an impact on the safety of the subject, as determined by the Investigator.
- Poor compliance with the visit schedule or medication intake in the previous BRV study.
- Participation in any clinical study of another investigation drug or device during the study.
- Pregnant or lactating woman.

If the Investigator has any medically valid reason to doubt the eligibility of a subject, the subject should not be included into the study. If, however, the Investigator has any other kind of doubts concerning the subject's eligibility, he/she should consult the UCB Study Physician or representative for clarification.

9.3 Subject Withdrawal

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

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, liver enzymes significant increase, and any other significant safety reason.
- Subject and/or Investigator does not think that the investigational drug is effective (i.e., lack or loss of efficacy).
- Lost to follow-up.
- Withdrawal of consent for personal reasons; not related to AE or lack/loss of efficacy.
- Other reason that has to be specified in the CRF.

Withdrawal criteria for already enrolled subjects who did not complete a Columbia Suicide Severity Rating Scale (C-SSRS) assessment at Screening:

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

Investigators should attempt to obtain information on subjects, in case of withdrawal or discontinuation. The Investigator should make every effort, and document his/her effort, to complete the EDV and preferably also the Down-Titration Phone Call and 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 also attempt to minimize the number of subjects lost to follow-up and to obtain a maximum of information on such subjects. The Investigator should make every 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.

10. TREATMENT OF SUBJECTS (INVESTIGATIONAL PRODUCT AND CONCOMITANT MEDICATIONS)

10.1 Study Investigational Products

10.1.1 Description of all Investigational Products

Oral tablets of 10 and 25mg BRV will be used in this study.

Investigational product (study drug) is prepared and stored at the UCB Clinical Trial Supplies (CTS) Operations or designee prior to shipment to the sites.

An Interactive Voice Response System (IVRS) will be used during this study. A telephone call to the system will be made:

- At the EV: for assignment of the study subject number and dispensing of initial medication

and

- At subsequent visits: for dispensing study medication
- To update the status of the subject when the subject leaves the study

The IVRS will also be applied for the ordering of the drug shipments to the sites via the UCB CTS Operations or designee, using a "trigger and re-supply" method of medication management specified in a separate document.

10.1.1.1 Dosing Schedule

The suggested individual starting dose of each subject will be 100mg/day.
The daily dose should be divided into 2 equal intakes (morning and evening), taken with or without food. The first intake will be in the evening of the day of the dispensation of the study medication.

At each subject visit, if necessary, the dosage can be adapted:

- Up-titration can be made by increments of a maximum 50mg/day on a weekly basis and up to a maximum dose of 200mg/day.
- Dose decreases can be made by steps of maximum 50mg/day on a weekly basis. In case of study drug discontinuation, a last down-titration step at 20mg/day for 1 week will be included prior to the study-drug free period.

The doses administered in this study must comply with doses that can be administered with either BRV 10mg tablets, 25mg tablets, or a combination of these 2 strengths in a total daily dose that can be administered in 2 equal doses. Daily dose prescriptions that do not respect these limitations should not be administered.

The supplies needed by the subject in terms of the number of bottles of each dosage (10mg and 25mg tablets) according to the dose prescribed and the possibility to down-titrate/up-titrate by a maximum of 50mg/day step, will be evaluated, as closely as possible at each visit.

In case the subject will not continue with BRV, the Investigator will plan the progressive down-titration of the study drug as described above. The down-titration period will be followed by a period free of study drug of minimum 2 weeks and a maximum of 4 weeks and subsequently the FV will occur.

At the time of study termination by the Sponsor (as defined in Section 8.4), subjects will discontinue the study drug following the described down-titration process or 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 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.

10.1.2 Packaging

Oral tablets of 10mg and 25mg BRV tablets will be packaged in bottles of 200 tablets. The Investigator will be supplied with a sufficient number of bottles and each bottle will have a unique, pre-printed identification number.

The Investigator will inform each subject on how to take the drug and that a possible excess of drug might be dispensed at each visit.

10.1.3 Labeling

Clinical drug supplies will be labeled in accordance with the current ICH guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any locally required statements.

The labels will be adapted to local regulatory requirements and the size of the investigational product package and will be translated as appropriate.

The label will consist of 2 parts. The first is a tear-off sticker which must be attached to the Case Report Form at the time of visit and the second remains fixed to the investigational product package. The subject number, subject initials and dispensation date will be added manually by the Investigator before dispensing.

10.1.4 Storage Requirements

Investigational product packages should be stored in a secured limited access area and maintained at the storage temperature specified on the investigational product package label. A recording of this controlled temperature should be done on site. If the storage conditions are not controlled (with recording), a temperature log should be completed at least once a week with the minimal and the maximal temperatures reached in the week preceding the record. Any excursion from the allowed temperature range will be communicated to the Sponsor or representative.

Storage should be in a pharmacy or in a locked facility. Supplies for this study will be stored in such a way that they may not be mixed up with supplies being used for another study. A standard storage statement will appear on each investigational product package label of study medication.

The Investigator or the hospital pharmacist is responsible for the appropriate storage and documentation of investigational product package at the site. The Investigator will instruct the subject/legally acceptable representative to store the medication at the storage temperature specified on the investigational product package label, in a secure place out of the reach of children.

10.1.5 Monitoring of Subject Compliance

At each visit after drug is dispensed, subjects must return all unused medication and the original investigational product package (even if empty). Drug reconciliation must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen.

The number of tablets as well as explanations of non-compliance must all be recorded on the CRF.

The Investigator will assess compliance during the study. Compliance with study medication is defined as investigational product consumption by the subject within 80% to 120% of the prescribed dosage.

10.1.6 Investigational Products Accountability

The Sponsor or its representatives will supply a Drug Accountability Form to be kept up-to-date by recording all study drug received during the course of the study and study drug released for subject use. Details of any drug lost (due to breakage or wastage), not used, disposed of at the study site or returned must also be recorded. All supplies and pharmacy documentation must be made available throughout the study for the Sponsor or designee to review.

The Drug Accountability Form should include the following:

- Number of tablets dispensed to and return by each subject, with the subject's number bottle number.
- Initials of the person who actually dispensed and/or received the return tablets.
- Dates of the above.
- Explanations for non-compliance.

Periodically and after completion of the study, all used (including empty bottles) and unused investigational product package must be reconciled and returned (preferably in their original package) to the Sponsor or designee according to a procedure to be defined at the time. Clinical drug supplies designated for the study cannot be used for any other purpose than that described in this protocol.

10.2 Concomitant Treatments and Rescue Medications

Should any treatment other than BRV be used, an accurate record must be kept in the clinic chart (source documentation) and the Case Report Form. This record should include the brand name of the drug, the dose, frequency, route, the indication for use and the date(s) of administration.

10.2.1 Permitted Concomitant Treatments (Medications and Therapies)

Subjects entering the present study in BRV monotherapy may require re-conversion from BRV monotherapy treatment to adjunctive treatment with BRV and another AED.
In this case, as well as for subjects entering the study in add-on, the Investigator may adapt the concomitant AED drug/dosage for safety or efficacy reasons.

In case of excellent efficacy and tolerability of BRV, withdrawal of concomitant AED(s) resulting in monotherapy with BRV may be re-attempted by the Investigator.

Benzodiazepines (BZD) are allowed. If taken more than once a week (for any indication) BZDs will be considered as a concomitant AED.

Use of phenobarbital and primidone is allowed.

Use of felbamate is permitted if continuous exposure is at least 18 months before Visit 1.

Use of VNS is also allowed.

10.2.2 Prohibited Concomitant Treatments (Medications and Therapies)

Vigabatrin.

11. STUDY PROCEDURES

11.1 Description of Procedures

11.1.1 Informed Consent

Prior to any study activities, subjects will be asked to read and sign an informed consent form that has been approved by an IEC/IRB and which complies with regulatory requirements. Subjects 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, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Where legally acceptable, a Partner Pregnancy Consent Form will be issued in case the partner of a male subject becomes pregnant (Section 12.1.6).

11.1.2 Subject Study Card

The Sponsor will provide to each Investigator an appropriate quantity of subject study cards that contains the Investigator's contact information in case of emergency. These subject cards will be in the language of the subject. The Investigator will fill in each card with his/her contact details (name and telephone number) and the subject's identifier. This card will be distributed to the subject at the EV. The Investigator will instruct the subject to keep the card with them all times.

11.1.3 Eligibility Criteria Assessment

The subject's eligibility will be assessed based on the eligibility criteria defined in the protocol.

11.1.4 Demography

At the EV, the subject's date of birth, gender, racial group and ethnicity will be recorded. Genetic differences among different racial groups in terms of hepatic enzymes, receptors and other factors might result in different pharmacokinetic, pharmacodynamic and/or drug responses. These differences may result in different dosing recommendations for different races. Therefore race designation will be collected for potential future compound labeling. In some countries, such as [redacted] recording the complete date of birth is not permitted.

11.1.5 Childbearing Potential and Birth Control

At the first visit, information on childbearing potential and contraceptive method used by female subjects will be collected. During the course of the study, the Investigator should make sure that birth control remains optimal should the subject's status change. A pregnancy test will be performed as specified in the Study Flowchart (see Table 5:1).

11.1.6 Medical and Procedure History

The General Medical and Procedure History will be obtained from the database of the previous study in which the subject was participating.

11.1.7 Epilepsy History

The history of epilepsy reported in the previous study in which the subject was enrolled will be considered as the history of epilepsy for the present study, and will be obtained from the database of the previous study.

11.1.8 Antiepileptic Medication History

The AED medication history will be obtained from the database of the previous study in which the subject was participating. The AED being used concurrently, at the current dose, will be recorded on the concomitant AED medication page of the CRF.

11.1.9 Vital Signs

At every office visit, 5 minutes supine or sitting pulse rate and blood pressure will be obtained followed by a standing pulse rate and blood pressure.

Vital signs for the EV will be obtained from the database of the last Evaluation Visit of the previous study.

11.1.10 Body Weight and Height

Body weight (subject wearing light clothing without shoes) will be obtained at the following visits: EV, each FEV, each YEV, EDV, and at the FV.

Body weight for the EV will be obtained from the database of the last Evaluation Visit of the previous study.

Height will be obtained at the EV. For subjects who are still potentially growing, height will also be measured at each YEV and the FV.

11.1.11 Physical Examination

A standard physical examination will be performed at the following visits: FEV, each YEV, EDV and at the FV. This examination may include investigation of skin, eyes, ear, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, musculoskeletal system and optionally genitourinary system.

The physical examination for the EV will be obtained from the database of the last Evaluation Visit of the previous study.

11.1.12 Neurological Examination

A standard neurological examination will be performed at the following visits: FEV, each YEV, EDV and at the FV. This examination will consist of a brief review of cortical functions, cranial nerves, motor function, reflex function, sensory function, gait and stance. Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairments and behavioral symptoms.

The neurological examination for the EV will be obtained from the database of the last Evaluation Visit of the previous study.

11.1.13 ECG

Following ethical approval of Protocol Amendment 2 and once the subject has signed the updated Informed Consent, the number of standard 12-lead ECGs will be reduced to once per year at each YEV and at the following visits: EDV and FV (in case the FV follows an EDV and the EDV ECG is normal, no additional ECG has to be performed at the FV).

At the EV, the ECG will be obtained electronically from the last Evaluation Visit of the previous study and should not be recorded in the CRF. 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.

11.1.14 Daily Record Card

At the EV, every FEV, every MEV, YEV, and the EDV, the subject will receive a Daily Record Card (DRC) and will be asked to come back at the next visit with the completed DRC.

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

epileptic seizures according to the ILAE codes and record the seizure types and frequency on the CRF; he/she will also confirm the presence of adverse events (if applicable). The concomitant medication changes and adverse events will be reported by the Investigator on the specific pages of the CRF.

The DRC will be considered source documentation. The subject should be educated to complete the DRC on a regular basis (each time that a seizure, an undesirable event, a modification of medication or investigational product, or a medical visit occurs).

Information on the following assessments collected in the DRC and transcribed to the appropriate CRF page are to be collected during the first 2 years:

- Healthcare provider consultations not foreseen by the protocol
- Workdays or schooldays lost by the subject
- Days subject received help from a caregiver (paid or not) at home

11.1.15 Laboratory Assessments and Study Medication/AED(s) Plasma Levels

At the following visits, FEV, YEV, EDV, and FV, laboratory assessments will be conducted using standard methods at a central laboratory. At the EV, data will be obtained from the last Evaluation Visit of the previous study and should not be recorded on the CRF. 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 back to the central laboratory.

Results for hematology, chemistry, urinalysis and pregnancy tests will be provided by fax to the Investigator.

The total blood volume drawn for the clinical laboratory assessments will be a maximum of 20mL/sampling. The subject should preferably be fasting. Study medication intake must not be delayed.

The following laboratory assessments will be conducted:

- Blood chemistry: glucose, urea, creatinine, sodium, potassium, calcium, phosphorus (inorganic), total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase (ASAT/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALAT/SGPT), gamma-glutamyltranspeptidase, and uric acid.
- The creatinine clearance (Cr Cl) will be calculated by the Cockroft'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.

- Hematology: white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, lymphocytes (number, %), monocytes (number, %), neutrophils (number, %), eosinophils (number, %), basophils (number, %).
- Urinalysis: specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, nitrites, leukocytes. If the test for protein, blood or leukocytes shows a trace or is positive, sediment and microscopic analyses (erythrocyte cast, leukocyte casts, hemoglobin casts, uric acid crystals, bihydrate calcium oxalate crystals, monohydrate calcium oxalate crystals, triple phosphate crystals and bacteria) will be conducted.
- Where applicable (women of childbearing potential), a serum pregnancy test will be conducted.

Cholesterol testing and plasma samples to analyze BRV and concomitant AED concentrations will be collected up to approval of Protocol Amendment 2.

11.1.16 Adverse Events (AEs)

At the EV, the Investigator will record any AE that was still ongoing at the end of the previous study in the source documentation. From the EV onwards, adverse events will be assessed at each visit and recorded in the CRF and in the source documents. The study participant will be given the opportunity to report AEs spontaneously. A general prompt will also be given to detect AEs, e.g., "Did you notice anything unusual about your health (since your last visit)?" In addition, the Investigator should review any self-assessment procedures (e.g. DRCs) used in the study.

11.1.17 Assessment of Suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of assessments (see Section 5.1).

11.1.18 Medical Procedures

From the EV onwards, collection of data on medical procedures (surgery, therapeutic and/or diagnostic, hospitalizations) undertaken during the study will be obtained. ECGs 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.

11.1.19 Non-Antiepileptic and Antiepileptic Concomitant Medications

At the EV, the Investigator will record all Non-Antiepileptic and Antiepileptic Concomitant Medications that were still ongoing at the end of the previous study. All medications (including over-the-counter preparations) taken during the course of the study must be documented in the CRF (brand name, indication, dosage, and the dates of start and discontinuation).

At each visit, a complete listing of all medications currently being taken will be obtained. Any changes, additions or deletions in the administration of non-antiepileptic concomitant medications must be recorded on the Non-Antiepileptic Concomitant Medications page of the CRF. In case of intake of forbidden concomitant medication (see Section 10.2) during the study period, the Investigator will contact the monitor immediately.

Changes, additions or deletions in the administration of antiepileptic concomitant medications must be recorded on the Antiepileptic Concomitant Medications page of the CRF.

11.1.20 Patient Reported Outcomes

A Patient Reported Outcomes (PRO) booklet per visit will be created for the FEV, YEV as well as for EDV. The assessment of the PROs will be limited to the first 2 years after study entry. These booklets will include, in order of appearance: The Patient Weighted Quality of Life in Epilepsy Inventory-- 31 item form (QOLIE-31-P - Version 2), the Hospital Anxiety and Depression Scale (HADS), and the EQ-5D self-report questionnaire. The PRO booklet is to be provided to subjects who are not mentally impaired, at the very beginning of the study visit. The subject will be asked to complete the questionnaires on his/her own. Once completed, the subject will hand back the booklet to the Investigator who will check that all questions have been answered.

The PRO booklets will be considered as part of the CRF as well as source documentation.

11.1.20.1 Quality of Life in Epilepsy Questionnaire (QOLIE-31-P)

QOLIE-31-P (Cramer and Van Hammée, 2003) (see Appendix17.1) is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998) that includes 7 subscales (seizure worry, overall quality of life, emotional well-being, energy-fatigue, cognitive functioning, medication effects, social function) and the health status item. Subscale scores as well as Total score range from 0 to 100 with higher scores indicating better health related quality of life. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to grade his or her overall "distress" related to the topic of each subscale. The QOLIE-31-P also contains an item asking about the relative importance of each subscale

topic. The subjects will complete the QOLIE-31-P at every FEV and YEV for the first 2 years, and at the EDV if the EDV occurs within the first 2 years.

11.1.20.2 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (Herrmann, 1997) (see Appendix 17.2) will be used to evaluate anxiety and depression/depressed feelings. The HADS was developed as a self-administered scale to assess the presence and severity of both anxiety and depression simultaneously. 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) will be calculated as recommended by the authors with each score ranging from 0 to 21 and higher scores indicating higher depression/anxiety. The subjects will complete the HADS at every FEV and YEV for the first 2 years, and at the EDV if the EDV occurs within the first 2 years.

11.1.20.3 EQ-5D Questionnaire

The EQ-5D (EuroQol Group, 2000) (see Appendix 17.3) is a self-administered questionnaire designed to measure health status. EQ-5D defines health in terms of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension is divided into 3 levels:

- no problem = 1
- some or moderate problems = 2
- extreme problems = 3

EQ-5D also captures a self-rating of health status on a 20cm vertical visual analogue scale, anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

The EQ-5D questionnaire will be assessed at every FEV and YEV for the first 2 years, and at the EDV if the EDV occurs within the first 2 years.

11.1.21 Hospital Stay

After the EV onwards, the collection of data on hospital stay will be assessed in the CRF. It includes the reason of hospitalization, the admission wards, transfer and length of stay. Hospital stays will be assessed at every FEV, MEV, YEV, and Additional Visit (AV) for the first 2 years, and at the EDV and the FV if these visits occur within the first 2 years.

11.1.22 Healthcare Provider Consultations not foreseen by the Protocol

After the EV onwards, healthcare provider consultations not foreseen by the protocol will be assessed and recorded in the CRF. This includes the type of provider (general practitioner, specialist physician, nurse), site of care (offsite vs private, office vs hospital, home, ER), and

the reason leading to the consultation. Healthcare provider consultations not foreseen by the protocol will be assessed at every FEV, MEV, YEV, and AV for the first 2 years, and at the EDV and the FV if these visits occur within the first 2 years.

11.1.23 Socio-professional Data

Socio-professional data will be collected at the YEV for the first 2 years and at the EDV and the FV if these visits occur within the first 2 years. This module collects information such as education level, housing status, employment status, need for caregiver and driving license. In countries such as [redacted] collection of these data is not permitted; therefore they will not be collected.

11.1.24 End of Study

The end of the subject's participation in the study will be confirmed on the subject's status evaluation section of the CRF. All data about the subject's status (study completion or reason for early study termination) will be recorded. It will be specified:

- Whether the subject completed (participated until the study was stopped) or prematurely discontinued from the study.

A subject will be considered lost to follow-up following 2 unsuccessful documented attempts to contact the subject (e.g. by telephone).

If a subject will not continue with the study drug, the Investigator will first schedule an EDV which will be followed by a progressive down-titration of the study drug. The dose decrease can be made by 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 study drug free period. At the end of the down-titration period, a phone call will be given to subjects having down-titrated from doses higher than 20mg/day. The Down-Titration Period will be followed by a period free of study drug at the minimum of 2 weeks and a maximum of 4 weeks and subsequently the FV will occur.

When the time point is reached at which the study will be terminated by the Sponsor (as defined in Section 8.4), subjects will discontinue the study drug, following the above described down-titration process or will be converted without down-titration to commercial BRV if, when and where available. Alternatively, subjects may transition to 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.

11.2 Description Visit by Visit

The EV will be performed on the same day as the last visit of the previous study in which the subject was enrolled. Should an interval become necessary between the last visit of the previous study and the EV in the present study, the Sponsor's Study Physician or representative should be contacted for agreement. The adverse events, medical procedures, non-antiepileptic and antiepileptic concomitant medication belonging to the interim period will be reported in the CRF, on specific pages.

Each visit will be planned within a "window" of ± 7 days from the previous visit. When possible, out of window visits should be rescheduled with respect to the EV.

At any time, the subject may have an additional study visit/phone call if the Investigator of the subject deems it necessary. All information, including the reason for the visit/phone call, any information on adverse events, etc., should be collected in the source documents and recorded in the appropriate section of the CRF.

11.2.1 Entry Visit

- Signing and dating of written informed consent.
- Dispensation of "clinical study subject card" (participation in the study).
- Verification of the inclusion/exclusion criteria.
- Demographic data.
- Childbearing potential.
- Body height.
- Dispensation of subject DRC and instruction on proper completion.
- Concomitant medications (AED and Non-AED) documentation.
- Recording of adverse events.
- Medical procedures.
- Dispensation of study medication (only dispensed once all inclusion/exclusion criteria have been met).
- Appointment for the next visit according to the schedule described in Section 5.2.

The following data will be obtained from the database of the Baseline Visit of the previous study and should not be recorded in the CRF:

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

The following data will be obtained from the database of the final Evaluation Visit of the previous study, and should not be recorded in the CRF/DRC:

- Vital signs including blood pressure and pulse rate.
- Body weight.
- Physical examination.
- Neurological examination.

- ECG.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis).
- Pregnancy test (if applicable); concomitant AED plasma levels and BRV plasma levels.
- Recording of seizures.

11.2.2 Full Evaluation Visit

- Vital signs including blood pressure and pulse rate.
- Body weight.
- Physical and neurological examination.
- Retrieval of previous subject DRC.
- Recording of seizures.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis); pregnancy test (if applicable); concomitant AED plasma levels and BRV plasma levels up to approval of Protocol Amendment 2.
- Recording of adverse events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and Non-AED) documentation.
- Drug return/accountability including study medication intake and compliance check.
- Dispensation of new DRC.
- Dispensation of study medication.
- Appointment for the next visit according to the schedule described in Section 5.2.

The following assessments will be performed during the first 2 years:

- QOLIE-31-P questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit.
- HADS questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit, after the QOLIE-31-P.
- Healthcare provider consultation not foreseen by the protocol.
- Recording of workdays and schooldays lost and days subject received help from a caregiver (paid or not) at home.
- Hospital stay.
- EQ-5D questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit, after the QOLIE-31-P.

11.2.3 Minimal Evaluation Visit

- Vital signs including blood pressure and pulse rate.
- Retrieval of previous subject DRC.
- Recording of seizures.

- Recording of adverse events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and Non-AED) documentation.
- Drug return/accountability including study medication intake and compliance check.
- Dispensation of new DRC.
- Dispensation of study medication.
- Appointment for the next visit according to the schedule described in Section 5.2.

The following assessments will be performed during the first 2 years:

- Healthcare provider consultation not foreseen by the protocol.
- Recording of workdays and schooldays lost and days subject received help from a caregiver (paid or not) at home.
- Hospital stay.

11.2.4 Yearly Evaluation Visit (replaces the first FEV of each year)

- Vital signs including blood pressure and pulse rate.
- Body weight and height (only for those subjects still potentially growing).
- Physical and neurological examination.
- ECG.
- Retrieval of previous subject DRC.
- Recording of seizures.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis); pregnancy test (if applicable); concomitant AED plasma levels and BRV plasma levels up to approval of Protocol Amendment 2.
- Recording of adverse events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and Non-AED) documentation.
- Drug return/accountability including study medication intake and compliance check.
- Dispensation of new DRC.
- Dispensation of study medication.
- Appointment for the next visit according to the schedule described in Section 5.2.

The following assessments will be performed during the first 2 years:

- QOLIE-31-P questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit.
- HADS questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit, after the QOLIE-31-P.

- Healthcare provider consultation not foreseen by the protocol.
- Recording of workdays and schooldays lost and days subject received help from a caregiver (paid or not) at home.
- Hospital stay.
- EQ-5D questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit, after the QOLIE-31-P.
- Socio-professional data.

11.2.5 Early Discontinuation Visit

- Vital signs including blood pressure and pulse rate.
- Body weight.
- Physical and neurological examination.
- ECG.
- Retrieval of previous subject DRC.
- Recording of seizures.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis); pregnancy test (if applicable); concomitant AED plasma levels and BRV plasma levels up to approval of Protocol Amendment 2.
- Recording of adverse events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and Non-AED) documentation.
- Drug return/accountability including study medication intake and compliance check.
- Dispensation of new DRC.
- Dispensation of study medication with down-titration dosing schedule.
- Appointment for the next visit according to the schedule described in Section 5.2.

Down-titration may not be applicable to subjects who may transition to another BRV study or may be initiated in a managed access program or similar type of program.

The following assessments will be performed only if the EDV occurs within the first 2 years:

- QOLIE-31-P questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit.
- HADS questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit, after the QOLIE-31-P.
- Healthcare provider consultation not foreseen by the protocol.
- Recording of workdays and schooldays lost and days subject received help from a caregiver (paid or not) at home.
- Hospital stay.

- EQ-5D questionnaire (except if subject is mentally impaired). The questionnaire should be filled in at the beginning of the visit, after the QOLIE-31-P.
- Socio-professional data.

11.2.6 Down-Titration Phone Call

- Recording of adverse events.
- Reminder of appointment for the next visit according to the schedule described in Section 5.2.

11.2.7 Final Visit (FV following a Study Drug Free Period after an EDV or FV initiated upon Sponsor request at the end of the program)

- Vital signs including blood pressure and pulse.
- Body weight and height (only for those subjects still potentially growing).
- Physical and neurological examination.
- ECG (except if the FV follows an EDV where ECG results were normal).
- Retrieval of previous subject DRC.
- Recording of seizures.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis); pregnancy test (if applicable); concomitant AED plasma levels and BRV plasma levels up to approval of Protocol Amendment 2 (except if the FV follows an EDV where laboratory results were normal).
- Recording of adverse events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and Non-AED) documentation.
- Drug return/accountability including study medication intake and compliance check.
- Completion of end of study status.
- Retrieval of "Clinical Study Subject Card".

The following assessments will be performed during the first 2 years:

- Healthcare provider consultation not foreseen by the protocol.
- Recording of workdays and schooldays lost and days subject received help from a caregiver (paid or not) at home.
- Hospital stay.
- Socio-professional data.

11.2.8 Additional Visit

At any time, the subject may have an additional study visit/phone call if the Investigator or the subject deems it necessary. All information, including reason for visit/phone call, any information on AEs, etc., should be collected in the source documents and recorded in the appropriate section of the CRF. Study medication can be dispensed if required.

If an additional office visit is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the office visit. If an additional office visit is conducted for reasons other than safety or efficacy concerns (e.g., 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 office visits.

11.3 Handling of Biological Samples

The safety samples (hematology, biochemistry, urinalysis, pregnancy test) will be routinely assayed and the results sent by fax and letter to the Investigators as specified in Section 11.1.15.

11.4 Other Supplies

Not applicable.

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1 Adverse Events

12.1.1 Definition of Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An adverse event 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 or undesirable experiences occurring during the study (i.e., after signature of the Informed Consent), including any pre- and post-treatment periods required by the protocol, must be reported in the CRF even if no investigational product was taken but specific study procedures were conducted. These include 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.

12.1.2 Procedures for Reporting and Recording Adverse Events

The study participant will be given the opportunity to report adverse events spontaneously. A general prompt will also be given to detect adverse events, e.g.

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

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

12.1.3 Description of AEs

The following guidelines and definitions should be used by the Investigator for the description of an AE when reporting information:

Nature of the AE:	Preferably an overall diagnosis or syndrome, rather than individual symptoms or signs. The Investigator must report adverse events using standard medical

	terminology. The CRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (e.g., diary card) and the corresponding medical terminology should be clarified in the source documentation.
Date of onset:	Date the AE started.
Intensity:	
Mild	The subject is aware of the sign or symptom (syndrome), but it does not interfere with his/her usual activities and/or it is of no clinical consequence.
Moderate	The AE interferes with the usual activities of the subject or it is of some clinical consequence.
Severe	The subject is unable to work normally or to carry out his/her usual activities, or the AE is of definite clinical consequence.
Actions taken with investigational product:	
Not applicable	For AEs occurring during the investigational product free period (pre and post-treatment periods and for single dose studies).
No change	Investigational product dosing remained the same in spite of the AE being present.
Dose increased	Investigational product dose was increased because of this AE.
Dose decreased	Investigational product dose was decreased because of this AE.
Temporarily discontinued	Investigational product was temporarily discontinued because of this AE, either because the subject chose to discontinue the investigational product or the physician felt it was in the subject's best interest to temporarily discontinue the investigational product.
Permanently discontinued	Investigational product was permanently discontinued because of this AE, either because the subject chose to discontinue the investigational product or the physician felt it was in the subject's best interest to discontinue the investigational product.
Other actions taken	
None	No other action was taken for this AE.
Medication	The subject took a medication (either prescription or non-prescription) specifically for this AE or existing medication dosage was modified.
Hospitalization or prolongation of hospitalization	Subject was hospitalized for this AE or subject's stay in hospital was prolonged because of this AE.

Therapeutic or diagnostic procedure	Subject used other therapeutic measures (e.g. ice, heating pad, brace, cast, etc.) or subject underwent a diagnostic procedure (e.g., additional lab test, x-ray, etc.) for this AE.
Date of outcome	Date the AE abated. If the AE consists of several signs and symptoms (syndromes), the sign or symptom with the longest duration determines the duration of the AE.

Outcome:

Resolved	The AE is no longer present at any intensity - completely abated.
Resolved with sequelae	The AE is resolved but residual effects are still present.
Ongoing	The AE is still present at the last contact with the subject.
Worsened	The AE is still present but at a heightened intensity. The rule of repetition of AE reporting should be applied.
Fatal	This AE caused or directly contributed to the subject's death.

Relationship to investigational product:

None	Only applicable when no investigational product was taken or when the subject is taking single-blind placebo, or when the AE can be ascribed with reasonable certainty to another cause.
Unlikely	There are good reasons to think that there is no relationship e.g., the AE is a known adverse drug reaction of a concomitant medication, **or the same AE does not reappear after re-administration of the investigational product.**
Possible	Equally valid arguments can be considered for or against an implication of the investigational product, For example, the AE: • follows a reasonable temporal sequence from the administration of the investigational product; • follows a known or expected response pattern to the investigational product; • but could readily have been produced by a number of other factors.
Probable	The relationship is likely. For example, the AE: • follows a reasonable temporal sequence from administration of the investigational product; • follows a known or expected response pattern to the investigational product; • is confirmed by improvement on stopping or

	reducing the dosage of the investigational product; • could not be reasonably explained by the known characteristics of the subject's clinical state.
Highly probable	There is a strong relationship. For example, the AE: • follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissues; • follows a known or expected response pattern to the investigational product; • is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance on repeated exposure (rechallenge).

12.1.4 Follow-up on Adverse Events

If an AE is still ongoing at the end of the study for a subject, a follow-up report should be provided until resolution/stable level of sequelae or the Investigator no longer feels it is clinically significant. If no follow-up report is provided, the Investigator must provide a justification. The follow-up will be continued for 30 days after the subject has completed the study or until the pre-analysis meeting, whatever is shorter.

12.1.5 Rule for Repetition of an AE

An increase in the intensity of an AE should lead to the repetition of the AE reporting 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,
- the AE verbatim being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first 1.

12.1.6 Pregnancy

Should a subject become pregnant during the course of the study, UCB should be informed immediately. The subject should be excluded from the study as soon as pregnancy is known (e.g. immediate start of down-titration of investigational product intake). The Investigator must inform the subject about the potential risk of malformations that may be caused by any AED, and about the available alternatives, e.g. voluntary termination with medical indication.

The pregnancy will be documented in the AE section of the CRF. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using UCB Investigator Pregnancy Report form in which the Investigator has to report on the health of the mother and

of the offspring. The health of the child must 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. A pregnancy is also potentially a SAE if it is the consequence of a hormonal birth control method failure.

In cases where the partner of a currently enrolled male subject 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 where legally acceptable. If the partner agrees to provide additional information, the UCB Investigator Pregnancy Report form will be forwarded to the subject's partner for completion.

12.1.7 Overdose of Investigational Product

Any daily intake of BRV beyond 200mg, the maximum dose used in this study, will be considered as overdose. Only symptomatic overdoses need to be recorded as AEs. 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. Excessive dosing (beyond that prescribed and including overdose) should be recorded in the study medication module.

12.1.8 Safety Signal Detection in Ongoing Clinical Studies

A regular monitoring of safety data collected during clinical studies will be performed as described in the Safety Signal Detection in Ongoing Clinical Trials Charter for BRV.

This ongoing monitoring of safety data will be performed at the product level.

Safety data including SAEs, AEs, vital signs, laboratory results and ECG data will be periodically reviewed by UCB on an ongoing basis.

The data from all studies with BRV will be scrutinized to detect as early as possible any safety concern related to the investigational product so that the Investigators, the clinical study subjects, the Regulatory Authorities and the Ethics Committees would be informed in the most appropriate manner.

12.2 Serious Adverse Events

12.2.1 Definition of Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose

- results in death;

- is life threatening;
- requires in-subject hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect.

In this context, the term life threatening refers to an event in which the subject was at immediate risk of death at the time of the event; it does NOT refer to an event which might have caused death if it would have been more severe.

Any important medical event that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition above should also be reported as a SAE. Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Cases of cancer should be reported as SAE following the criteria "Important medical event".

Hospitalization criteria are met anytime a subject is formally admitted to hospital, regardless of duration, or if a subject is kept in hospital overnight and it is not clear if a formal admission took place. If a subject is taken to a hospital and neither of the above apply (e.g. an ER visit), an event may still be considered serious, meeting the criteria of medically important.

Hospitalization for diagnostic or therapeutic procedures in the absence of any associated adverse event will not be considered as a SAE, except when otherwise required by Regulatory Authorities. If a hospitalization is planned prior to the subjects receiving the first dose of investigational product (at week 0), it will not be classified as either an AE or SAE. This also applies to situation of scheduled elective surgery where no AE is present. Non-complicated, preplanned elective surgery will not be considered an AE or SAE even if it involves hospitalization. However, if a hospitalization is unplanned or is a result of an adverse event, this will be considered an SAE.

Any event reported by the Investigator to the local authorities will follow the same reporting procedures as an SAE.

12.2.2 Procedures for Reporting Serious Adverse Events (SAEs)

If a SAE is reported, UCB or its representative must be informed within 24 hours of receipt of this information by the site (see contact information for SAEs reporting listed in Section 2). The Investigator must forward to UCB (or its representatives) 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.

A copy of the Investigator SAE report form and the completion guide will be provided to the Investigator. The Investigator SAE report form has to be completed in English.

Additional information (e.g. autopsy or lab reports) received by the Investigator must be provided within 24 hours. All documents in 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.

UCB (or its representatives) will communicate safety information (Suspected Unexpected Serious Adverse Reactions - SUSAR) 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 representatives with evidence of such IEC/IRB notification.

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 after the end of the study for each subject and to inform the participating subjects of the need to inform the Investigator of any SAE within this period. 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.

The reference document for the assessment of the expectedness of the SAEs is the Investigator's Brochure.

12.2.3 Follow-up of Serious Adverse Events

A SAE should be followed-up until it has resolved/has a stable of sequelae or the Investigator no longer feels it is clinically significant.

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

12.2.4 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 12.2.2.

13. STATISTICS

13.1 Statistical and Analytical Plans

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

13.1.1 Study Population(s)

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

The Efficacy Population 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.

13.1.2 Safety, Efficacy, and Other Variables

13.1.2.1 Primary Safety Variables

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

13.1.2.2 Other Safety Variables

- Laboratory tests (blood chemistry, hematology, and urinalysis)
- Vital signs (SBP, DBP, pulse rate) and body weight
- Electrocardiogram
- Physical and neurological examination
- 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

13.1.2.3 Secondary Efficacy Variables

- Percentage of subjects on continuous BRV monotherapy for at least 3 months, at least 6 months, and at least 12 months of the Evaluation Period

13.1.2.4 Other Efficacy Variables

- Partial onset seizure (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
- 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
- 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
- EuroQoL-5 Dimensions questionnaire response for each assessment for the first 2 years for the Evaluation Period and for the last assessment during the first 2 years of the Evaluation Period

13.1.2.5 Pharmacoeconomic Variables

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and ER visits) during the first 2 years of the Evaluation Period
- Indirect costs (workdays or schooldays lost by the subject and days subject received help from a caregiver) 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

13.1.2.6 Pharmacokinetic Variables

- Brivaracetam (parent compound only) plasma levels
- Concomitant AED (and/or relevant metabolites) plasma levels

13.1.3 Statistical Evaluation

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.

For the purpose of statistical analysis, the following periods are considered:
- Evaluation Period (V1 until the last Evaluation Visit)
- Down-Titration Period
- Post-Treatment Period

13.1.3.1 Evaluation of Safety

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®) 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.

Changes in laboratory values, vital signs, and weight will be summarized by visit. Possibly clinically significant treatment-emergent abnormalities for laboratory values, vital signs, and weight will be listed and summarized by analysis period. Electrocardiogram abnormalities, as well as physical and neurological abnormalities, will be presented in subject data listings.

13.1.3.2 Evaluation of Efficacy

13.1.3.2.1 Efficacy Analyses

All efficacy analyses will be based on the Efficacy Population. All efficacy variables will be analyzed descriptively. The Baseline of an efficacy variable will be the Baseline from the previous study.

The secondary efficacy variables for the cumulative proportion of subjects remaining on BRV monotherapy from the start of the study through 3, 6, and 12 months will be estimated using Kaplan-Meier methods.

13.1.3.2.2 Other Efficacy Analyses

The percentage reduction in 28-day POS frequency relative to Baseline will be summarized using descriptive statistics. Baseline will be defined as the Baseline value from the previous study. Additionally, the number and percentage of subjects continuously seizure-free during the Evaluation Period will be presented. Descriptive statistics for the change in QOLIE-31-P and EQ-5D from Baseline of the previous study to each visit during the first 2 years of the study and the last Evaluation Period Visit will also be presented.

13.2 Determination of the Sample Size

For this open-label, LTFU study, no sample size calculation has been performed. The sample size will depend upon recruitment into and completion of proceeding studies; approximately 300 - 600 subjects were expected.

13.3 Changes in the Conduct of the Study or the Planned Analyses

An SAP will be developed and approved prior to the database lock. The full details of the statistical analyses will be provided in the SAP. Any deviations from the SAP as well as changes from the protocol will be discussed in the Clinical Study Report.

13.4 Statistical and Analytical Issues

13.4.1 Adjustments for Covariates and Interactions

No adjustment for covariates is foreseen.

13.4.2 Handling of Dropouts of Missing Data

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

Since subjects will drop out at different times from the study, the results will be presented by categories of duration of exposure where applicable.

13.4.3 Interim Analysis

Due to the single-arm open-label nature of this study, no interim analysis as such will be performed. However, interim database locks will have to 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, SDR) applying to the entire BRV program is organized.

13.4.4 Multi-center Studies

No analysis by center is planned.

13.4.5 Multiple Treatment Comparisons/Multiple Endpoints

Not applicable.

13.4.6 Examination of Subgroups

No inferential analyses are planned. Only descriptive summaries will be made on sub-groups of subjects with similar exposure.

13.5 Pre-Analysis Review of Data

A pre-analysis review will take place:

- before starting analysis.
- after all the data have been verified / coded / entered into the database.

The review will be performed to decide how to deal with problems in subject's data (missing values, withdrawals, protocol deviation).

After the pre-analysis review and documentation of all decisions concerning the subjects with problems, the database will be locked.

The analysis will start after the approval and locking of the database, and approval of the final SAP.

13.6 Criteria for Un-blinding the Results

Not applicable

13.7 Dictionaries

Adverse events and concomitant procedures will be coded according to MedDRA dictionary (latest available version).

Medications will be coded according to World Health Organization Drug dictionary (latest available version).

14. ETHICS AND REGULATORY REQUIREMENTS

14.1 Approval

The final protocol and any amendments must be signed by the Principal Investigator of the site and by appropriate representative(s) of UCB.

The final protocol must be submitted to and approved by:

- a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB).
- the relevant Regulatory Authorities, according to local regulations.

If any alterations to the protocol are required by these bodies, they can be implemented only with the written agreement of the Investigator and the Sponsor's approver(s) before further submission to the requesting body.

A copy of the IEC/IRB's written approval with clear identification of the submitted document(s) and a list of members attending the meeting (listed by function and affiliation) should be forwarded by the Investigator to the Clinical Trial Manager (CTM).

The usual composition of the IRB/IEC (or DHHS number) along with an IRB/IEC Statement of Compliance should also be forwarded to the CTM.

Before submission to an IRB/IEC, the consent form and any other written information to be provided to subjects (e.g., advertisement) must be submitted for internal Sponsor approval. The study is not allowed to start until the protocol and related documents (informed consent, advertisement, etc.) have received written approval from the IEC/IRB and Regulatory Authorities, if applicable, as well as until other GCP prerequisites are fulfilled.

If new information becomes available, it should be communicated without delay to the subject, the Investigator, the IEC/IRB, and regulatory authorities, wherever required.

The IEC/IRB must be notified promptly by the Investigator (or Sponsor, if applicable) in writing of the following:

- Deviations from, or changes to the protocol to eliminate immediate hazards to all the study subjects.
- Significant changes to the conduct of the study. Significant changes to the protocol can only be affected by a formal protocol amendment that must be submitted to the IEC/IRB and approved prior to implementation at the site.
- New information that may adversely affect subject safety or the conduct of the study.

The Investigator (or Sponsor, if applicable) should comply with the applicable regulatory requirements related to the reporting of safety information to the IEC/IRB and Regulatory Authorities.

14.2 Subject Information and Consent

Adequate information will be provided to the subject in both oral and written form and consent will be obtained in writing prior to performance of any study specific procedure. Where required, the consent form or a specific Assent Form will be signed and dated by minors. The content and process of obtaining informed consent will be in accordance with all applicable regulatory and IEC/IRB requirements.

UCB may provide a sample informed consent form and a subject information sheet. The final consent form must be approved by the IEC/IRB and should contain the applicable ICH-GCP elements in a language readily understood by the subject (i.e., lay terminology) and/or subject's legally representative(s).

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 IEC/IRB and use of the amended form.

For [redacted] centers, a separate Health Insurance Portability and Accountability Act (HIPAA) agreement may be used if required by the IRB or institution.

Subjects and/or subjects' legally acceptable representatives will be informed of the purpose of the study in unambiguous language they easily understand. Their participation is voluntary and they can at any time decide to stop their participation without any influence on their future care or treatment. The subjects and/or subject's legally acceptable representatives must be informed about the main procedures used to guarantee their anonymity, especially during the analysis of their personal data. Subjects and/or subjects' legally acceptable representatives should be able to ask any questions about the study and to receive relevant answers. They will receive complete written information in the Subject Information Sheet or Informed Consent Form.

After having received extensive information about the purpose and risks of the study and having had enough time to consider participation in the study, the subject and/or subject's legally acceptable representative(s) must give their written consent by signing and dating the Informed Consent Form. This form will also be signed and dated by the person who obtained the informed consent and then retained by the Investigator. Obtaining of consent will be confirmed in the subject's medical records. The subject and/or subject's legally acceptable representative(s) will receive a copy of the signed and dated consent form and the original will be filed in the Investigator's Study File.

If the signature of a witness is required, the witness should sign and personally date the consent form after the subject and/or subject's legally acceptable representative(s) has signed. By signing the consent form, the witness attests that the information in the consent form and in any other written information was accurately explained to, and apparently understood by, the subject and/or subject's legally acceptable representative(s)and that informed consent was freely given.

The subject and/or subject's legally acceptable representative(s) may withdraw their consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she and/or his/her legally acceptable representative(s) have signed the informed consent form. A Case Report Form must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her and/or his/her legally acceptable representative(s)written consent to participate in the study.

If any new information that could influence the subject and/or subject's legally acceptable representative(s) decision to stay in the study becomes available, this information will be transmitted to the subject and/or subject's legally acceptable representative(s) without delay. In addition, the informed consent form must be amended accordingly or a separate consent form be created and submitted to the IEC/IRB for approval prior to being implemented for re-consent of all ongoing subjects and/or subjects' legally acceptable representative(s) in the study and for use in consenting all subjects entering the study from that point forward.

14.3 Subject Confidentiality

Subject confidentiality will be maintained at all times. Personnel from UCB (or its representative), from Regulatory Authorities and members of the IEC/IRB may inspect medical records and Case Report Forms for verification of the accuracy of data. These groups are obliged to respect medical secrecy and to refrain from divulging the subject's identity or any other personal information. Sites will be required to obliterate any possibly identifying information (e.g., name, social security number, address, etc.) on any materials, forms, or report prior to sending them to the Sponsor or its designee.

Medical records will be handled by professional standards and existing local laws.

14.4 Informing the General Practitioner

If the subject agrees, the Investigator may inform the subject's regular physician of his/her participation in the study, by sending him/her the letter to the General Practitioner (GP). A template letter will be proposed by UCB.

15. STUDY MANAGEMENT AND ADMINISTRATION

15.1 Monitoring

Monitoring of the study is the responsibility of UCB and may be delegated to a Clinical Research Organization (CRO) or a contract monitor. The Monitor (the individual responsible for monitoring) will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP, and all applicable regulatory requirements.

The Investigator will allow UCB or its representatives to review periodically, at mutually convenient times during the study and after the study has been completed, all CRFs and corresponding source documents (e.g., portions of office, hospital and laboratory records for each study participant). Therefore, the monitor will have direct access to these records. The monitoring visits provide UCB or its representatives with the opportunity to evaluate the progress of the study, to 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.

15.2 Direct Access to Source Data/Documents

The Investigator(s)/Institution(s) will permit study-related monitoring, audits by or on behalf of UCB, IEC/IRB review, and regulatory inspection(s), providing direct access to source data/documents.

Source documents are original records in which raw data are first recorded. These may be: hospital/clinic/GP records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, Quality of Life Questionnaires, etc. 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:

- Demographic data
- Childbearing potential and birth control
- Vital signs
- Body weight and height
- Physical and neurological examinations
- Socio-professional data
- Number of school/workdays lost

Original laboratory results, ECG, will be inserted in the CRF and are also to be considered as source data. Original DRCs, QOLIE-31-P, EQ-5D, and HADS questionnaires will be retrieved. The site will keep a copy in the CRF and this copy will considered as 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 correcting fluid or have temporary attachments (such as removable self-stick notes). Photocopies of case report forms are not considered acceptable source documents. Photocopies will only be considered as acceptable source documents when used to establish permanent documentation of data captured on non-permanent media.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (e.g. 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.

For subjects exposed to 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 subject/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.

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

15.3 Audit and Inspection

The Investigator will permit study-related audits by auditors 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 (i.e. signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with the planned arrangements, the protocol, facility and IEC/IRB 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.

15.4 Case Report Forms (CRF) and Screen Failures

Data reflecting participant experience with the drug(s) under investigation will be reported to UCB. These data will be recorded on the Case Report Forms (CRF). The CRF is essentially a data entry form and may not routinely constitute the original (or source) medical record. CRF should be kept in a secure, limited access area.

The CRF will be organized in yearly books. CRFs will be signed and dated by the Principal Investigator or a Co-Investigator designated by the Principal Investigator. The Investigator's or Co-Investigator's signature on the CRF attests to its accuracy and completeness. Paper CRFs will be completed in dark ballpoint pen, and must be legible. If an entry in a CRF needs to be changed, the correction will be made as follows:

- Cross-out the initial entry (must still be legible).
- Write the correct entry next to it together with your initials, the date and justification if necessary. Correcting fluid, erasure or any form of obliteration of data in CRFs is not permitted except to obliterate information that could specifically identify a subject (i.e., a name written on a subject diary).

UCB cannot interpret a blank answer as NONE or NA (not applicable); therefore, all fields must be completed. Please mark data which could not be recorded as follow: ND for "Not Done", NA for "Not Applicable", UN for "Unknown".

Data reported in the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained in those source documents.

The Investigator will keep a subject screening log to document identification of subjects who entered pre-study screening.

All supportive documentation submitted to UCB in addition to the Case Report Form, such as laboratory results or hospitalization records, must be clearly identified with the study number, study participant number, and study participant initials; any personal information, including the study participant's name, must be removed or rendered illegible to preserve individual confidentiality. All original lab reports will remain at the study site.

15.5 Adherence to Protocol

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 IEC/IRB. The Investigator/institution and the Sponsor will sign the protocol to confirm agreement.

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 CPM 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 IEC/IRB and the appropriate regulatory authorities, if applicable prior to being implemented.

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.

15.6 Investigator Site File

All documents required for the conduct of the study as specified in the ICH GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring, auditing by UCB or its designee and/or inspection.

15.7 Data Handling

UCB will be responsible for data processing and may delegate this responsibility to a CRO.

CRF data will be entered in a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. An electronic audit trail system will be used to track all data changes in the database subsequent to the reconciliation of the double-entered data. The SAS system will be used for the statistical analysis of the data. Regular back-ups of the electronic data will be performed.

15.8 Termination of 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;
- If applicable - return of treatment codes to UCB or its representatives;
- discussion/reminder on archiving responsibilities;
- discussion of IEC/IRB requirements for study termination;
- arrangements for unused CRFs, lab supplies and any other study related supplies.

In addition, 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, non-compliance, or unsatisfactory quality.

If the study is prematurely terminated or suspended, UCB or its representatives 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 IEC/IRB 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.

15.9 Clinical Study Report

UCB will prepare a clinical study report, in accordance with the relevant ICH guidelines. The report will include a thorough description of the clinical and laboratory methods, a discussion of the results and a list of all measurements as specified in the SAP. This report may be included in submissions to government drug regulatory authorities worldwide, or used for whatever reason considered appropriate by UCB. No information contained in the report may be used without written approval of UCB.

The coordinating Investigator(s) designated by UCB to sign the report (see Section 2) will have an opportunity to comment on the draft version. He/she must give his/her comments within 7 days of receiving the report. In addition, he/she will sign the report for approval within 7 days of receipt of the revised version or a satisfactory reply to these comments.

15.10 Insurance and Liability

UCB has taken out an insurance policy, for the total duration of the study, covering the subjects, in respect of the risks involved in this study according to this protocol. In the case of injury or disability deriving from participation in the study, the subject is requested to inform the treating physician responsible for the study without delay.

15.11 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 (ICH-GCP Guideline-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.

15.12 Allocation of Responsibilities

The Investigator is responsible for the implementation of the protocol but can delegate tasks to the research team. The Investigator remains responsible for coordinating and informing his/her staff about the protocol and any possible changes made to it. The Investigator should maintain a site signature and delegation of responsibility log. The list should be kept up to date.

15.13 Curriculum Vitae (CV)

A signed and dated FDA Form 1572, in addition to required local forms, and recent (updated every 2 years) CV (in English) are required from each Investigator showing a current affiliation with the research center. All sub-Investigators listed on the FDA Form 1572 should also date and sign a recent English version of their CVs. Any changes to the site personnel should be updated on a new FDA Form 1572.

15.14 Financial Disclosure

A financial disclosure statement must be obtained for everyone listed on the FDA form 1572. These must be collected before subject enrollment. The sites must inform the Sponsor if information related to financial disclosure changes during the course of the study and/or up to 1 year after study completion/end of the study.

15.15 Good Clinical Practice

Non-compliance 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 non-compliance may result in the termination of the participants' involvement in the study.

15.16 Disclosure of Clinical Study Information

UCB alone shall be responsible for the registration of clinical studies in a public studies registry and for the disclosure of study results on a publicly accessible website.

15.17 Publication

Authorship of planned manuscripts for submission to medical journals shall be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

The Site and its Investigators agree that if the Site is part of a multi-center Study, Site and Investigator(s) shall coordinate in advance any intended disclosure of the results of the study with UCB to ensure that the results of individual sites are not published or presented before those of the multi-centre Study, unless otherwise agreed by in writing by UCB.

Subject to the following paragraph, the authors have the final responsibility for the content of their own publication(s) and the decision to submit it/them for publication.

Any planned manuscript, presentation, abstract or other intended disclosure of the results of the study or otherwise originating from the study shall be made available for review to UCB at least thirty (30) days before submission for publication or any other means of disclosure in order to allow UCB to protect its intellectual property.

In the rare event that such disclosure would affect the patentability of any invention to which UCB has rights, UCB shall have the right to request an additional delay to the proposed disclosure of no more than ninety (90) days so as to allow UCB to preserve its intellectual property.

16. REFERENCES

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

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.

N01315 Protocol Amendment 3 Integrated

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	25-Mar-2015 17:32 GMT+01
[redacted]	Clinical Approval	25-Mar-2015 17:33 GMT+01