1 TITLE

PROTOCOL N01199

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

Sponsor:

UCB Pharma Inc.
1950 Lake Park Drive
USA - GA 30080
Smyrna
UNITED STATES

Hereafter "UCB"

Brivaracetam - IND Number: 70,205

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Protocol Signatures:
Authorized signature on behalf of UCB:

Principal Investigator
"By my signature below, I acknowledge that I have read the protocol RPCE05C2110 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 the Sponsor of the clinical study or its representatives(s)."

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4 LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
AED(s)	Antiepileptic Drug(s)
ALT (ALAT/SGPT)	Alanine Aminotransferase
ASAT/SGOT	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
AV	Additional Visit
b.i.d.	Twice Daily
BRV	Brivaracetam
BZD	Benzodiazepine
CBZ	Carbamazepine
CDMS	Clinical Data Management System
CPMP	Committee for Proprietary Medicinal Product
Cr Cl	Creatinine Clearance
CRF	Case Report Form
CRO	Clinical Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTM	Clinical Trial Manager
CV	Curriculum Vitae
CYP	Cytochrome
DBP	Diastolic blood pressure
DHHS	Department of Health and Human Services
dl	Deciliter
DRC	Daily Record Card
DTP	Down-titration Phone Call
ECG	Electrocardiogram
EDV	Early Discontinuation Visit
EQ-5D	EuroQoL 5 Dimensions Questionnaire
ER	Emergency room
EV	Entry Visit
FEV	Full Evaluation Visit
FDA	Food and Drug Administration
FV	Final Visit
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyltranspeptidase
GMP	Good Manufacturing Practices
GP	General Practitioner
h	Hour
HADS	Hospital Anxiety and Depression Scale

HDPE	High Density Polyethylene
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	Kilogram
L	Liter
LTG	Lamotrigine
m	Meter
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MEV	Minimal Evaluation Visit
µg	Microgram
mg	Milligram
min	Minute
ml	Milliliter
µL	Microliter
µM	Micromol
PBO	Placebo
PGS	Primary Generalized Epilepsy
PK	Pharmacokinetics
POS	Partial Onset Seizure
PRO	Patient Reported Outcomes
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Questionnaire
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SBP	Systolic blood pressure
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Study Physician
SV2A	Synaptic Vesicle Protein 2A
TMF	Trial Master File
WBC	White Blood Cell
WHO	World Health Organization

YEV	Yearly Evaluation Visit

5 PROTOCOL SUMMARY

Investigational Product:
Brivaracetam (BRV)

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

Secondary Objective
To evaluate the maintenance of efficacy over time of BRV (for POS/PGS subjects).

Exploratory Objectives
- To explore the effects of BRV on the subject's Health-related Quality of Life, anxiety, and depression for the first 2 years.
- To explore medical resource use and indirect cost parameters for the first 2 years.
- To obtain a description of the subject's self-reported health status for the first 2 years.
- To explore any change in the subject's socio-professional status for the first 2 years.

This study will provide subjects suffering from epilepsy, who may benefit from BRV as adjunctive treatment, the opportunity to receive open label adjunctive BRV treatment. Conversion to monotherapy is not permitted anymore; however, subjects already on monotherapy are allowed to continue BRV monotherapy. The access will be limited to the subjects having completed a previous BRV study as listed in Section 5.2.

Estimated Number of Subjects, Sites and Rationale:
It is estimated that approximately 500 - 1,000 subjects will enter the study based on the assumption that 90% of subjects having completed a previous study with BRV as adjunctive treatment in epilepsy will roll over into the present study.

It is estimated that between 100 - 200 sites will participate in this global protocol.

Subject Population and Diagnosis:
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.
- Subjects with epilepsy who participated in previous BRV studies which allow access to the present study.
- Subjects from whom the Investigator believes a reasonable 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 30 µg [or 50 µg if associated with other antiepileptic drugs (AEDs) 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. According to the judgment of the Investigator, 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 or laboratory values which may have an impact on the safety of the subject.
- 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.

Drug Administration:
Subjects coming from BRV studies have the opportunity to access BRV treatment at a flexible dose of up to a maximum of 200 mg/day in b.i.d. administration. It is recommended that the daily dose be divided equally and be taken with or without food. The first intake will be in the evening of the day of the dispensation of the study medication. The individual starting dose of each subject will be the one defined/reached at the end of the previous study.

At each visit, an interactive voice response system (IVRS) /interactive web response system (IWRS) will be responsible for issuing subjects kits of study medication, as appropriate, according to the visit schedule and according to the supplies needed by the subject in terms of the number of tablets of each size (80 count or 200 count), and of each dosage (10 mg and 25

mg tablets) according to the dose prescribed and the possibility to down-titrate/up-titrate by a maximum of 50 mg/day steps 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. Containers of 80 tablets will be progressively removed.

Oral tablets of 10 mg and 25 mg BRV will be used in this study. Initially, BRV 2.5 mg and 10 mg tablets were packaged in blister cards containing 20 tablets each. Visit cartons of 80 (4 blister cards) and 200 (10 blister cards) tablets were provided and each visit carton had a unique, pre-printed identification number.

In November 2006, a transition from blister cards to HDPE (High Density Polyethylene) bottles was implemented. Brivaracetam 2.5 mg oral tablets were packaged in bottles of 200 tablets and BRV 10 mg oral tablets were packaged in bottles of 80 and 200 tablets. Each bottle has a unique, pre-printed identification number. Containers of 80 tablets will be progressively removed.

HDPE bottles containing 80 and 200 oral tablets of BRV 25 mg will be available when subjects begin enrolling from BRV Phase III studies (N01252, N01253, and N01254). Containers of 80 tablets will be progressively removed.

Each subject will be informed on how to take the drug and that there is an excess of drug in the visit carton or bottle.

Methodology:
This is a Phase III, therapeutic long-term follow-up, multicenter, non-comparative, open-label and single arm study.

This study will run throughout the duration of the clinical development period of BRV and will thus include the therapeutic exploratory study completed during the early stage of development as well as therapeutic confirmatory studies which will be completed in the later stages of development. For this reason, the study design of this study and in particular the frequency of study visits is adapted for the 2 types of phases as described below.

For those subjects coming from the therapeutic exploratory study, visits will be scheduled as follows:

- First year:
  - During the first 6 months there will be 1 visit/month; 1 Full Evaluation Visit (FEV) alternating with 1 Minimal Evaluation Visit (MEV).
  - During the next 6 months there will be 1 visit every 3 months; 2 FEV (at V7 and V8).
- Second and subsequent years:
  - 1 visit every 3 months; 1 FEV alternating with 1 MEV.

- The Yearly Evaluation Visit (YEV) will be performed in replacement of the first FEV of each year.

For those subjects coming from therapeutic confirmatory studies:

- 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/3 months: FEV alternating with MEV.
  - The YEV will be performed in replacement of the first FEV of each year.

Variables and Assessments:

The efficacy variables will be assessed by using the seizure count information recorded on the DRC. The subject will be asked to record the date and the number (where possible) of epileptic seizures he/she has experienced. The type of seizure (according to individual description of seizures) will be defined by the Investigator by adding the ILAE codes. The Investigator will also confirm on the DRC the number of seizures of each type experienced by the subject.

The periods considered in the definition of efficacy variables are the following:

- 3-month periods over the Evaluation Period (V1 until the last evaluation visit).

Primary safety variables:

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

Other safety variables:

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

- 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

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

Other efficacy variables

For subjects with focal-onset epilepsy:

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

For subjects with generalized epilepsy:

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

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

- Change in 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

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

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and emergency room [ER] visits) during the first 2 years of the Evaluation Period
- Indirect costs (work days or school days 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

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) [a]	Down-Titration Phone Call (DTP) [a]	Final Visit (FV)	Reference to Section
ASSESSMENTS									
Written Informed Consent	X								11.1.1
Clinical Trial Subject Card Dispensing	X								11.1.2
Verification Inclusion/ Exclusion Criteria	X								9.1 and 9.2
Demographic Data	X								11.1.3
Childbearing Potential	X								11.1.4
Medical and Procedures History	X[b]								11.1.5
Epilepsy History	X[b]								11.1.6
AED History	X[b]								11.1.7
Vital Signs	X[c]	X	X	X	X	X		X	11.1.8
Weight and Height[d]	X	X		X		X		X	11.1.9
Physical Examination	X[c]	X		X		X		X	11.1.10
Neurological Examination	X[c]	X		X		X		X	11.1.11
ECG[e]	X[c]			X		X		X	11.1.12
Daily Record Card Dispensed	X	X	X	X		X			11.1.13
Daily Record Card Retrieval	X	X	X	X		X		X	11.1.13
Recording of Seizures	X[c]	X	X	X		X		X	11.1.13
QOLIE-31-P[f] [k]		X		X		X			11.1.20
HADS[f] [k]		X		X		X			11.1.21

Table 5:1 Study Flowchart (continued)

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit[a] (EDV)	Down-Titration Phone Call (DTP)[a]	Final Visit (FV)	Reference to Section
EQ-5D[g] [k]		X		X		X			11.1.22
Workdays and schooldays lost / days with caregiver's help[k]		X	X	X	X	X		X	11.1.13
Hospital Stay[k]		X	X	X	X	X		X	11.1.23
Heathcare Provider Consultations not foreseen by the protocol[k]		X	X	X	X	X		X	11.1.24
Socio-professional Data[h] [k]				X		X			11.1.25
Laboratory Assessments[i]	X[c]	X		X		X		X	11.1.14
Recording of Adverse Events	X	X	X	X	X	X	X	X	11.1.15
C-SSRS[i]		X	X	X	X	X		X	11.1.16
Medical Procedures	X	X	X	X	X	X		X	11.1.17
Concomitant AED	X	X	X	X	X	X		X	11.1.18
Concomitant Non-AED	X	X	X	X	X	X		X	11.1.18
Drug Dispensing	X	X	X	X		X			10.1.2 and 10.1.6
Drug Return/Accountability		X	X	X		X		X	10.1.6 and 10.1.7
End of Study Status[j]								X	11.1.26

Table 5:1 Study Flowchart (continued)

AED=antiepileptic drug; AV=Additional Visit; CRF=Case Report Form; C-SSRS=Columbia Suicide Severity Rating Scale; DTP=Down-titration Phone Call; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; HADS=Hospital Anxiety and Depression Scale; 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 transferred 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 transferred from the database of the last visit of the previous study and should not be recorded in the CRF: Vital Signs, Physical Examination, Neurological Examination, ECG, Recording of seizures, Laboratory Assessment including Safety (blood chemistry, hematology and urinalysis)
(d) Height will be recorded at Visit 1 (Entry Visit). Height will also be measured at each YEV and the Final Visit for those subjects that are still potentially growing.
(e) At Final Visit, ECG is mandatory except if Final Visit follows an Early Discontinuation Visit where ECG results were normal.
(f) QOLIE-31-P and HADS are to be completed at the beginning of the visit by all subjects (except those coming from N01193) who are not mentally impaired.
(g) EQ-5D questionnaire is to be completed by all subjects (except those coming from N01193) who are not mentally impaired.
(h) Socio-professional data will be collected for all subjects except those coming from N01193.
(i) Laboratory assessment includes blood chemistry, hematology and urine analysis; where applicable (women of childbearing potential), a urine pregnancy test will be done. Laboratory assessment is mandatory at Final visit except if Final Visit follows an Early Discontinuation Visit where laboratory results were normal.
(j) 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).
(k) Procedures only performed during the first 2 years of -subject participation in the study (eg, until last scheduled visit [Y3-YEV]) or EDV/FV in case the subject discontinues participation within the first 2 years).
(l) The C-SSRS assessment will be implemented by site per IRB/IEC approval and upon completion of required training. As of the time of Protocol Amendment 6, all subjects had completed their Entry Visit. Thus, the C-SSRS was not assessed for any subjects at their Entry Visit.
(m) 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

For subjects coming from the therapeutic exploratory study (N01193), visits will be scheduled as follows:

- First year:
  - During the first 6 months there will be 1 visit/month; 1 Full Evaluation Visit (FEV) alternating with 1 Minimal Evaluation Visit (MEV).
  - During the next 6 months there will be 1 visit every 3 months; 2 FEV (at V7 and V8).
- Second and subsequent years:
  - 1 visit every 3 months; 1 FEV alternating with 1 MEV.
  - The Yearly Evaluation Visit (YEV) will be performed in replacement of the first FEV of each year.

For those subjects coming from therapeutic confirmatory studies (N01252, N01253, and N01254):

- 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 Diagrams

Subjects coming from Exploratory Study (N01193)		
1st Year Follow-up		
Month	**Visit**	**Type of Visit**
M0	V1	Entry Visit
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV
M4	V5	FEV
M5	V6	MEV
M6	V7	FEV
M7		
M8		
M9	V8	FEV
M10		
M11		
2nd and subsequent years follow-up		
M12	V9	YEV
M15	V10	MEV1
M18	V11	FEV
M21	V12	MEV2

Subjects coming from Confirmatory Studies (N01252, N01253, N01254)		
1st Year Follow-up		
Month	**Visit**	**Type of Visit**
M0	V1	Entry Visit
M1	V2	MEV
M2	V3	FEV
M3	V4	MEV
M4		
M5		
M6	V5	FEV
M7		
M8		
M9	V6	MEV
M10		
M11		
2nd and subsequent years follow-up		
M12	V7	YEV
M15	V8	MEV1
M18	V9	FEV
M21	V10	MEV2

In case the subject will not continue with the study drug, the Investigator will first plan an Early Discontinuation Visit 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 50 mg/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 20 mg/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 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 one of the most common and challenging neurological disorders. It has been estimated that over 50 million people are affected worldwide (Engel and Pedley, 1998; 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 approximately 50 to 70 cases per 100.000. In developing countries, the figure is higher due to more limited obstetric services and the greater likelihood of cerebral infection and trauma. The incidence varies greatly with age, with high rates occurring in childhood, falling to low levels in early adult life, but with a second peak in those aged over 65 years. In many people, particularly children, the condition may remit, although a significant proportion will have epilepsy lifelong. The disease duration is often determined by the underlying cause. Sudden unexpected death, a complication of great concern, occurs in 1 to 5 per 1000 patient years, particularly if the seizure disorder remains uncontrolled. The treatment for epilepsy remains difficult, and there is ongoing medical need for new antiepileptic drugs (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 (ie, related to a focal brain dysfunction), which are the most frequent and account for approximately 60 to 70% of all cases, and generalized epilepsy syndromes, which represent approximately 25 to 30% of all epilepsy syndromes. In about 10% of cases, other specific syndromes are classified or the classification remains uncertain.

The classification of epileptic syndromes and seizure types is – and always was – a matter of ongoing debate. First published in 1960 and last updated officially in 1981 for seizures and 1989 for epilepsies (Commission on Classification and Terminology of the 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. Like levetiracetam (LEV, Keppra®), BRV displays a high and selective interaction with a novel brain-specific binding site, SV2A (synaptic vesicle protein 2A). However, the binding affinity of BRV for SV2A is approximately 10-fold higher than with LEV. This binding site appears to be the major target for its pharmacological activity. Unlike LEV, BRV also reduces voltage-dependent sodium currents. Brivaracetam also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid, and glycine-induced currents. Brivaracetam is extensively metabolized, but seizure protection appears to be associated with the parent compound.

Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of BRV absorption is not affected by food. The pharmacokinetics (PK) are dose-proportional (at least from 10 mg to 600 mg). Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5 L/kg, a value that is close to that of total body water. The plasma half-life of BRV is approximately 8 hours in young healthy male adults. The main metabolic pathway of BRV is by hydrolysis of the acetamide group to the corresponding carboxylic acid, while a second pathway is the ω1-hydroxylation mediated by CYP2C19 (with contributions of several other isoenzymes). The combination of these 2 pathways results in the hydroxyacid terminal metabolite. These metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, with less than 9% as unchanged BRV, is excreted in urine within 72 hours after dosing.

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

Brivaracetam does not impair the efficacy of oral contraceptives containing ethinylestradiol 30 µg and levonorgestrel 150 µg. Brivaracetam does not induce CYP3A4 using midazolam as a marker probe. Brivaracetam has no interaction on lamotrigine (LTG) 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 (CBZ), lamotrigine, LEV, oxcarbamazepine metabolite, phenobarbital, phenytoin, topiramate, valproate, and zonisamide. Carbamazepine epoxide was significantly increased from baseline at all BRV doses greater than 20 mg/day, nearly reaching the upper limit of normal (3.0 µg/mL) at BRV doses of 100 and 150 mg/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 100 mg/day.

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

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

For additional details on safety and efficacy of BRV, please refer to the Investigator's Brochure (UCB reference code RXCE06E2216).

6.5 Study Rationale

The Sponsor wishes to develop BRV as an adjunctive antiepileptic treatment in subjects 16 years and older suffering from epilepsy. N01199 will give subjects who have participated in previous BRV adjunctive treatment studies in epilepsy the opportunity to access adjunctive BRV treatment under the present protocol. Conversion to monotherapy is not permitted anymore; however, subjects already on monotherapy are allowed to continue BRV monotherapy.

The subjects allowed to enter the study will mainly suffer from partial onset seizures (subjects coming from N01193, N01252, N01253, and N01254 [UCB protocol reference code RPCE06G0706]), while a minority will present with generalized epilepsy (subjects coming from N01254). The N01252, N01253 and N01254 studies aimed to test the efficacy and tolerability of BRV in POS subjects as oral therapy. This study will explore the long-term safety and efficacy of BRV in such a population.

6.5.1 Dose Selection

In this study, individualized doses up to a maximum of 200 mg/day will be used. Twice daily dosing is deemed necessary to ensure more regular exposure over the 24-hour interval.

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

6.5.2 Subjects Population

6.5.2.1 Minimal Age

Subjects 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 (CPMP/EWP/566/98 rev 1, 2000).

Depending on country-specific regulations, those subjects may be considered as adolescents or adults (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.

6.5.3 Duration of Treatment

For each subject, the 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.

Statement
The present study will be conducted in accordance with:

- This protocol.
- International Conference on Harmonization (ICH): ICH E6 Note for Guidance on Good Clinical Practice [CPMP/ICH/135/95] and Code of Federal Regulations on Good Clinical Practice (GCP) Title 21 Parts 50, 54, 56, 312 and 314).
- The principles that have their origin in the Declaration of Helsinki.
- All applicable local 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 200 mg/day in subjects suffering from epilepsy.

7.2 Secondary Objectives

To evaluate the maintenance of efficacy over time of BRV (for POS/PGS subjects).

7.3 Exploratory Objectives

- To explore the effects of BRV on the subject's Health-related Quality of Life, anxiety, and depression for the first 2 years.
- To explore medical resource use and indirect cost parameters for the first 2 years.
- To obtain a description of the subject's self-reported health status for the first 2 years.
- To explore any change in the subject's socio-professional status for the first 2 years.

8 STUDY DESIGN

8.1 Type/Design

This is a Phase III, therapeutic, long-term, follow-up, multicenter, noncomparative, open-label, and single arm study.

The study design of this study and in particular the frequency of study visits is adapted for the 2 types of studies as described below.

For those subjects coming from the therapeutic exploratory study (N01193), visits will be scheduled as follows:

- First year:
  - During the first 6 months there will be 1 visit/month; 1 Full Evaluation Visit (FEV) alternating with 1 Minimal Evaluation Visit (MEV).
  - During the next 6 months there will be 1 visit every 3 months; 2 FEV (at V7 and V8).
- Second and subsequent years:
  - 1 visit every 3 months; 1 FEV alternating with 1 MEV.
  - The Yearly Evaluation Visit (YEV) will be performed in replacement of the first FEV of each year.

For those subjects coming from therapeutic confirmatory studies (N01252, N01253, N01254):

- 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 Yearly Evaluation Visit will be performed in replacement of the first FEV of each year.

8.2 Subjects/Sites Numbers

It is estimated that approximately 500 - 1,000 subjects will enter the study based on the assumption that 90% of subjects having completed a previous study with BRV as adjunctive treatment in epilepsy will roll over into the present study.

It is estimated that between 100 - 200 sites will participate in the study.

8.3 Subject Identifier

Each subject will be identified by his/her initials and a subject identifier which include the study number, the site number and a sequential enrollment number. The Master CRF number will be used as an additional identifier on laboratory reports and at the level of the database.

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 of 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 the 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.
- Subjects with epilepsy who participated in previous BRV studies which allow access to the present study.
- Subjects from whom the Investigator believes a reasonable 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 30 µg [or 50 µg 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. According to the judgment of the Investigator, 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 or laboratory values which may have an impact on the safety of the subject.
- 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 (SP) or representative for clarification.

9.3 Subject Withdrawal

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 Early Discontinuation Visit and preferably also the Down-Titration Phone Call and the Final Visit. 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.

The study medication will be progressively down-titrated. During the down-titration period, the dose may be decreased in steps of a maximum of 50 mg/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. 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 will occur.

9.3.1 Withdrawal Criteria

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.

<u>Withdrawal criteria for already enrolled subjects who did not complete a C-SSRS assessment at screening:</u>

- 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.

9.3.2 Subject Replacement Policy

Not applicable.

10 TREATMENT OF SUBJECTS (INVESTIGATIONAL PRODUCT AND CONCOMITANT MEDICATIONS)

10.1 Study Investigational Products

10.1.1 Description of all Investigational Products

Active investigational product (tablets containing 10 or 25 mg BRV) will be supplied under the responsibility of the Sponsor Clinical Trial Supply Department for all subjects. The frequency at which investigational product will be supplied to each individual site will be adapted to the recruitment capacity of that site and to the expiry date of the investigational product.

10.1.2 Dosing Schedule

Subjects coming from BRV studies have the opportunity to access BRV treatment at a flexible dose of up to a maximum of 200 mg/day in b.i.d. administration. It is recommended that the daily dose be divided equally, taken with or without food, and that the first intake will be in the evening of the day of the dispensation of the study medication.

The individual starting dose of each subject will be the one defined/reached at the end of the previous study. It is recommended that the dosing be done in even increments such as 20 mg, 30 mg, 40 mg, etc. with the implementation of the IVRS/IWRS.

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

- Up-titration can be made by increments of maximum 50 mg/day on a weekly basis and this to a maximum of 200 mg/day.
- Dose decreases can be made by steps of maximum 50 mg/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 each visit, an IVRS/IWRS will be responsible for issuing subjects kits of study medication, as appropriate, according to the visit schedule and according to the supplies needed by the subject in terms of number of containers of each size (80 or 200) and of each dosage (10 mg or 25 mg tablets) according to the dose prescribed and the possibility to down-

titrate/up-titrate by a maximum of 50 mg/day steps. Containers of 80 tablets will be progressively removed.

In case the subject will not continue with BRV, the Investigator will plan the progressive down-titration of the study drug. 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 Final Visit 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, 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.

10.1.3 Packaging

Oral tablets of 10 mg and 25 mg BRV will be packaged in bottles of 80 and 200 tablets. Containers of 80 tablets will be progressively removed. On request via the IVRS/IWRS, the Investigator will be supplied with a sufficient number of containers. Each container will have a unique, pre-printed identification number.

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

10.1.4 Labeling

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

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

10.1.5 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.

10.1.6 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.

Compliance with study medication is defined as investigational product consumption by the subject within 80% - 120% of the prescribed dosage.

10.1.7 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 and carton or 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 cartons and 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

For any treatment other than BRV, 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)

Investigator may adapt the AED drug/dosage for safety or efficacy reasons. Benzodiazepines (BZD) taken more than once a week (for any indication) will be considered as a concomitant AED.

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 Entry Visit. The Investigator will instruct the subject to keep the card with them at all times.

11.1.3 Demography

At the first visit, date of birth, gender and racial group will be recorded.

11.1.4 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).

11.1.5 General Medical and Procedure History

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

11.1.6 Epilepsy History

The history of epilepsy reported at the first visit of the previous study in which the subject was enrolled will be considered as the history of epilepsy for the present study and will be directly electronically transferred from this study.

11.1.7 Antiepileptic Medication History

The AED medication history will be transferred 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.

11.1.8 Vital Signs

At every visit, after 5 minutes supine or sitting, pulse rate and blood pressure will be obtained followed by a standing pulse rate and blood pressure. At the Entry Visit, vital signs will be obtained electronically from the last Evaluation Visit of the previous study and should not be recorded in the CRF.

11.1.9 Weight and Height

Body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) will be obtained at the following visits: Entry Visit, each Full Evaluation Visit, each Yearly Evaluation Visit, Early Discontinuation Visit, and at the Final Visit. Height will be obtained at the Entry Visit. For subjects that are still potentially growing, height will also be measured at each Yearly Evaluation Visit and the Final Visit.

11.1.10 Physical Examination

A standard physical examination will be performed at the following visits: every Full Evaluation Visit, each Yearly Evaluation Visit, Early Discontinuation Visit and at the Final Visit. This examination may include investigation of skin, eyes, ear, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, musculoskeletal system and optionally genitourinary system. At the Entry Visit, the physical examination will be obtained electronically from the last Evaluation Visit of the previous study and should not be recorded in the CRF.

11.1.11 Neurological Examination

A standard neurological examination will be performed at the following visits: every Full Evaluation Visit, each Yearly Evaluation Visit, Early Discontinuation Visit and at the Final Visit. 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. At the Entry Visit, the neurological examination will be obtained electronically from the last Evaluation Visit of the previous study and should not be recorded in the CRF.

11.1.12 ECG

Once the subject has signed the updated Informed Consent, the number of standard 12-lead ECGs will be reduced to once per year at the following visits: Yearly Evaluation Visit, Early Discontinuation Visit, and Final Visit (in case the FV follows an EDV and the EDV ECG is normal, no additional ECG has to be performed at FV). At the Entry Visit, 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.

11.1.13 Daily Record Card (DRC)

At the Entry Visit, every Full Evaluation Visit, every Minimal Evaluation Visit, Yearly Evaluation Visit, and the Early Discontinuation Visit, 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 following information will be recorded on the DRC:

- Date and the number (where possible) of epileptic seizures
- Type of seizure (according to individual description of epileptic seizures)
- Occurrence of seizure clusters
- All unusual events concerning the subject's health
- Changes in concomitant medication (dosage and/or product)
- Changes in investigational product (dosage)

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 part of the CRF as well as 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).

11.1.14 Laboratory Assessments

At the following visits, Full Evaluation Visit, Yearly Evaluation Visit, Early Discontinuation Visit, and Final Visit, laboratory assessments will be conducted using standard methods at a central laboratory. At the Entry Visit, data will be transferred electronically 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 within 72 hours after sample receipt.

The total blood volume drawn for the clinical laboratory assessments will be a maximum of 20 ml/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 (ALP), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (ASAT/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALAT/SGPT), gamma-glutamyltranspeptidase (GGT), and uric acid.
- The creatinine clearance (Cr Cl) will be calculated by the Cockroft's formula (only at the Entry Visit):
    - 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 urine pregnancy test will be conducted.

Plasma samples to analyze BRV and concomitant AED plasma concentrations will no longer be obtained.

11.1.15 Adverse Events (AEs)

At the Entry Visit, the Investigator will record any adverse event that was still ongoing at the end of the previous study. From the entry Visit 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. daily record cards) used in the study.

11.1.16 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 (Section 5.1).

11.1.17 Medical Procedures

From the Entry Visit 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.

11.1.18 Non-Antiepileptic and Antiepileptic Concomitant Medications

At the Entry Visit, 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 prohibited concomitant medication (see Section 10.2.2) 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.

11.1.19 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 Patient Reported Outcomes will be limited to the first 2 years after study entry, which includes the YEV of Year 3. 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 that 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.

Subjects coming from N01193 will not have to complete the PRO booklet. All other subjects that are not mentally impaired will complete the PRO booklet at FEV, YEV and/or EDV for the first 2 years.

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

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

QOLIE-31-P (Cramer and Van Hammée, 2003) 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 Full Evaluation Visit and Yearly Evaluation Visit for the first 2 years, and at the Early Discontinuation Visit if the Early Discontinuation Visit occurs within the first 2 years.

11.1.21 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (Herrmann, 1997) 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 Full Evaluation Visit and Yearly Evaluation Visit for the first 2 years, and at the Early Discontinuation Visit if the Early Discontinuation Visit occurs within the first 2 years.

11.1.22 EQ-5D Questionnaire

The EQ-5D (EuroQol Group, 2000) 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 20 cm 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 Full Evaluation Visit and Yearly Evaluation Visit for the first 2 years, or at the Early Discontinuation Visit if the Early Discontinuation Visit occurs within the first 2 years.

11.1.23 Hospital Stay

From Entry Visit 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 Full Evaluation Visit, Minimal Evaluation Visit, and

Yearly Evaluation Visit, for the first 2 years, and at the Early Discontinuation Visit and the Final Visit if these visits occur within the first 2 years.

11.1.24 Healthcare Provider Consultation not Foreseen by Protocol

From Entry Visit onwards, healthcare provider consultation not foreseen by protocol will be assessed and recorded in the CRF. It will include the type of provider [general practitioner (GP), specialist physician, nurse], site of care (office-private, office-hospital, home, emergency room) and the reason leading to the consultation. Healthcare provider consultations not foreseen by the protocol will be assessed at every Full Evaluation Visit, Minimal Evaluation Visit, and Yearly Evaluation Visit for the first 2 years, and at the Early Discontinuation Visit and the Final Visit if these visits occur within the first 2 years.

11.1.25 Socio-professional Data

Socio-professional data will be collected at the Yearly Evaluation Visit for the first 2 years and/or at the Early Discontinuation Visit if the Early Discontinuation Visit occurs within the first 2 years in the CRF for subjects coming from N01252, N01253 and N01254 only. It collects information such as education level, housing status, employment status, need for caregiver and driving license.

11.1.26 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 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 Early Discontinuation Visit 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 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week will be included prior to the study-drug free period. At the end of the down-titration period, a Down-Titration Phone Call will occur for subjects having down-titrated from doses higher than 20 mg/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 Final Visit 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, 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 Entry Visit 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 entry visit 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.

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.
- Demography data: date of birth, gender and racial group.
- Childbearing potential.
- Medical and procedure history.
- Epilepsy history.
- AED history.
- Vital signs including blood pressure and pulse rate.
- Body weight and height.
- Physical and neurological examination.
- ECG.
- Dispensation of subject DRC and instruction on proper completion.
- Recording of seizures.
- Concomitant medications (AED and Non-AED) documentation.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis), pregnancy test (if applicable).
- 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 transferred 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 transferred from the database of the last evaluation visit of the previous study and should not be recorded in the CRF/DRC:

- Vital signs including blood pressure and pulse rate.
- Physical examination.
- Neurological examination.
- ECG.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis).
- Pregnancy test (if applicable).
- 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), urine pregnancy test (if applicable).
- 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 which includes the YEV in Year 3.

- QOLIE-31-P questionnaire (except if subject mentally impaired and except for all subjects coming from N01193). The questionnaire should be filled in at the beginning of the Visit.
- HADS questionnaire (except if subject mentally impaired and except for all subjects coming from N01193). The questionnaire should be filled in at the beginning of the Visit, after the QOLIE-31-P.
- Healthcare provider consultation not foreseen by 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 mentally impaired and except for all subjects coming from N01193).

11.2.3 Minimal Evaluation Visit

- Vital signs including blood pressure and pulse rate.
- Retrieval of previous subject DRC.
- Recording of seizures.
- Recording of workdays and schooldays lost and days subject received help from a caregiver (paid or not) at home during the first 2 years.
- Hospital stay during the first 2 years.
- Healthcare provider consultation not foreseen by protocol during the first 2 years.
- 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.

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), urine pregnancy test (if applicable).
- 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 which includes the YEV in Year 3.

- QOLIE-31-P questionnaire (except if subject mentally impaired and except for all subjects coming from N01193). The questionnaire should be filled in at the beginning of the Visit.
- HADS questionnaire (except if subject mentally impaired and except for all subjects coming from N01193). The questionnaire should be filled in at the beginning of the Visit, after the QOLIE-31-P.
- Healthcare provider consultation not foreseen by protocol
- Recording of workdays and school days lost and days subject received help from a caregiver (paid or not) at home.
- Hospital stay.
- EQ-5D questionnaire (except if subject mentally impaired and except for all subjects coming from N01193).
- 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), urine pregnancy test (if applicable).
- 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 mentally impaired and except for all subjects coming from N01193). The questionnaire should be filled in at the beginning of the Visit.
- HADS questionnaire (except if subject mentally impaired and except for all subjects coming from N01193). The questionnaire should be filled in at the beginning of the Visit, after the QOLIE-31-P.
- Healthcare provider consultation not foreseen by 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 mentally impaired and except for all subjects coming from N01193).
- 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 after an EDV when EDV ECG results were normal).
- Retrieval of previous subject DRC.
- Recording of seizures.
- Recording of workdays and school days lost and days subject received help from a caregiver (paid or not) at home during the first 2 years.
- Hospital stay during the first 2 years.

- Healthcare provider consultation not foreseen by protocol during the first 2 years.
- Laboratory assessment including safety (hematology, blood chemistry, and urinalysis), urine pregnancy test (if applicable).
- 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".

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.

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 11.1.14.

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 patient 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 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.
Pattern:	
Intermittent	The AE recurs with the same intensity at various intervals throughout the entire time period specified. There were intervals within the specified time period when the AE was not present.
Continuous	The AE is present at the same intensity for the entire time period specified. There was no time at which the event abated or was not present during the time period specified.

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.
Action taken with investigational product:	
Not applicable	For AEs occurring during the study drug free period.
No change	Investigational product dosing remained the same in spite of the AE being present.
Dosage increased	Investigational product dose was increased because of this AE.
Dosage 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 study drug 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 study drug or the physician felt it was in the subject's best interest to discontinue the investigational product.
Other actions taken:	If action taken other than study drug, the appropriate sections should be completed: Medications, Medical procedures.
Outcome:	
Resolved	The AE is no longer present at any intensity - completely abated.
Resolved with sequela	The AE is resolved but residual effects are still present.
Ongoing	The AE is still present at the last contact with the subject. If the AE is marked "ongoing", the outcome date should be blank.
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.
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. If the AE is marked "ongoing", the outcome date should be blank.
Relationship to study drug:	
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 (e.g., a gun shot wound).
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).
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. • 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 (re-challenge).

12.1.4 Follow-up on Adverse Events

If an AE is still ongoing at the time the CRF is collected, a follow-up report should be provided at a later date. If no follow-up report is provided, the Investigator must provide a justification.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplementary measurements and/or evaluations (e.g., re-challenge procedure).

A serious AE or an AE leading to premature discontinuation from the study must always be followed up until it has resolved or the Investigator no longer feels it is clinically significant.

12.1.5 Rule for Repetition of an AE

An unexpected 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 Investigator's original description of the AE being the same for the first and repeated AE.

12.1.6 Pregnancy

Should a subject become pregnant during the course of the study, the SP of the Sponsor should be informed immediately. The subject should be excluded from the study as soon as pregnancy is known (immediate start of down-titration of investigational product intake).

The pregnancy will be documented in the AE section of the CRF. The Investigator must inform the subject about the potential risk of malformations that may be caused by any AED, and about the available alternatives, eg, voluntary termination with medical indication. The progression of the pregnancy must be followed up using the standard Sponsor Pregnancy form. The Investigator has to report on the health of the mother and of the offspring.

In cases where the partner of a male subject enrolled 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 Pregnancy Report and Outcome form will be forwarded to the subject's partner for completion.

12.1.7 Overdose of Investigational Product

For this protocol, any daily intake of more than 200 mg/day will be considered as an overdose. Symptoms associated with an overdose must be recorded as AEs. Overdose without signs or symptoms will be documented in the "Study Medication Intake" section of the CRF.

12.2 Serious Adverse Events

12.2.1 Definition of Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that occurs at any dose:

- results in death.
- is life threatening, (an immediate risk of death).
- requires in-patient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability/incapacity (any severe or long-lasting inability to carry out normal work or normal activities).

or

- is a congenital anomaly/birth defect (in a child of a subject/patient who took the investigational product, especially of a mother who was pregnant during the study).

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 emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any event reported by the Investigator to the local authorities will follow the same reporting procedures as a "Serious Adverse Event".

Cases involving cancer as an Adverse Event could be reported as serious using the criterion "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. 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.

12.2.2 Procedures for Reporting Serious Adverse Events (SAE)

The Sponsor (or its representatives) must be informed about an SAE within 24 hours of the site knowing about the event (see contact details for SAEs listed in Section 2). The Investigator must promptly forward to the Sponsor (or its representatives) a duly completed "Investigator SAE report form" provided by the Sponsor, even if the data are incomplete or if it is obvious that more data will be needed to make any conclusions.

Additional information (e.g., autopsy or lab reports…) should be provided to the sponsor in a timely fashion to ensure accurate follow-up of each case. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the SAE report form.

The Sponsor (or its representatives) will communicate safety information to the appropriate agency(ies) 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. Investigators are to provide the Sponsor or its representatives with evidence of such IEC/IRB notification.

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

If known by the Investigator, Serious Adverse Events up to 30 days after withdrawal of study medication must be reported to the Sponsor, even if the Investigator is certain that they are in no way associated with the study drug. Adverse Events that the Investigator thinks may be associated with the study medication must be reported to the Sponsor 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 (IB).

12.2.3 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 serious AEs (including Anticipated SAEs) as detailed in Section 12.2.2.

13 STATISTICS

A general description of statistical methods is presented below. Additional details will be described in the Statistical Analysis Plan (SAP).

13.1 Statistical and Analytical Plans

13.1.1 Study Population(s)

- Subpopulations

There are 2 mutually exclusive subpopulations. They are defined based upon enrollment.

1. Partial onset seizure: Subjects enrolled from prior studies N01193, N01252, N01253, and subjects from N01254 with a diagnosis of POS at N01254 study entry
2. Primary generalized seizure: Subjects enrolled from prior study N01254 with a diagnosis of PGS at N01254 study entry

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

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

13.1.2 Efficacy and Safety Variables

Primary safety variables:

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

Other safety variables:

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

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

Other efficacy variables:

For subjects with focal-onset epilepsy:

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

For subjects with generalized epilepsy:

- Generalized (type II) seizure days per 28 days during the Evaluation Period
- Percent reduction in generalized (type II) seizure days per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate for generalized (type II) seizure days over the Evaluation Period. A responder is defined as a subject with a ≥50% reduction in seizure days from the Baseline Period of the previous study

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

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

- Change in 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

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

- Direct costs (healthcare provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations, and emergency room [ER] visits) during the first 2 years of the Evaluation Period
- Indirect costs (work days or school days 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

13.1.3 Statistical Evaluation

- General considerations:

Summary statistics will consist of frequency tables for categorical variables and descriptive statistics (number of available observations, mean, median, standard deviation, minimum, maximum, 25th and 75th percentiles) for continuous variables.

The periods considered are:

- Evaluation Period (V1 until the last Evaluation Visit)
- Down-Titration Period
- Post-Treatment Period

Efficacy summaries will be created separately for the POS and PGS subpopulations within the efficacy population, and safety summaries will be created for the safety population.

- Baseline:

Baseline, whether efficacy or safety, will always refer to the original prior study pretreatment Baseline value. Baselines created and validated, as part of the prior study SAPs, will be copied and used by this study for all changes from baseline analyses.

- Study entry/disposition:

Subjects will be sufficiently described to enable a clear understanding of the populations and subpopulations and relevant demographics, disease, medical history, current treatment(s), as well as disposition. Historical and Baseline data will be copied from the prior study as required by the SAP.

- Seizure efficacy variables:

Analyses will be based upon the Efficacy Population. Summaries will be over the entire Evaluation Period and by 3-month periods over the Evaluation Period.

- QOLIE-31-P, HADS, EQ-5D, and socio-professional efficacy variables:

Analyses will be based upon the Efficacy Population and summarized by data collection scheduled visits and for the last Evaluation Period assessment during the first 2 years. Data collected after Year 2 are not planned to be summarized.

- Medical resource and indirect cost efficacy variables:

Analyses will be based upon the Efficacy Population and summarized by 3-month periods. Data collected after Year 2 are not planned to be summarized.

- Safety variables:

Analyses will be based upon the Safety Population. Summary tables will be presented over the Evaluation Period by time windows, by periods, and by categories of total duration of exposure.

Treatment-emergent AEs will be summarized by categories of total duration of exposure, period, and Medical Dictionary for Regulatory Activities (MedDRA®) Primary System Organ Class (SOC), 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 for SAEs.

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

Hospital anxiety and depression scales will be analyzed for the POS and PGS subpopulations.

13.2 Determination of the Sample Size

No sample size calculation has been made. Sample size will depend upon recruitment into and completion of preceding studies; approximately 500 - 1000 subjects are expected.

13.3 Statistical and Analytical Issues

13.3.1 Handling of Dropouts of Missing Data

Safety and efficacy variables will be analyzed as they are available. Days with missing information will be ignored in the calculation of the seizure frequency and seizure days. Since subjects will drop out at different times from the study, results will be presented by categories of duration of exposure.

13.3.2 Interim Analysis and Data Monitoring

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

13.3.3 Use of an Efficacy Subset of Subjects

The efficacy population will be a subset of the safety population. The efficacy population will be divided into 2 mutually exclusive groups, the POS and PGS subpopulations. Additionally, as needed, the POS and the PGS subjects may be subset into categories that group subjects and subject data according to similar BRV exposure times.

13.3.4 Examination of Subgroups

Subgroup analyses, if performed, will be specified in the SAP.

13.4 Criteria for Starting the Analysis

A pre-analysis data review will take place before starting any formal analysis. A pre-analysis data review will follow pertinent UCB Standard Operating Procedures.

13.5 Dictionaries

Adverse events medical and surgical history will be coded according to the MedDRA. Coding of indications of concomitant medication has been stopped during the course of the study.

Medications will be coded according to WHO Drug dictionary.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Approval

The final protocol and any amendments must be signed by the Principal Investigator of the site, the Sponsor Study Physician, the Sponsor Clinical Lead, the Sponsor Clinical Trial Manager (CTM) and the Sponsor Statistician.

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, the Study Physician, the Clinical Lead, the Statistician, and CTM, and the sponsors' approvers 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 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

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

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

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. The content and process of obtaining informed consent will be in accordance with all applicable regulatory and IEC/IRB requirements.

For subjects already ongoing in the study, a new informed consent will be issued and need to be signed covering the increased risk of suicidality or suicidal thoughts to comply with the warning issued by the FDA subsequent to analysis performed on marketed anti-epileptic drugs. Although data from BRV studies were not included in FDA's analysis, this risk may be expected because BRV belongs to this class of medication.

The Sponsor 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).

The Investigator, or a person designated by the Investigator, should fully inform the subject about all pertinent aspects of the study including the fact that the protocol has been granted the approval of the IRB/IEC and local regulatory authorities if required.

Subjects 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 must be informed about the main procedures used to guarantee their anonymity, especially during the analysis of their personal data. They will receive complete written information in the Subject Information Sheet. Subjects should be able to ask any questions about the study and to receive relevant answers.

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 or their legal representative 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 will receive a copy of the signed and dated consent form and the original will be filed in the Investigator's Study File. The consent form or a specific assent form, where required, will be signed and dated by minors.

If the signature of a witness is required, the witness should sign and personally date the consent form after the subject 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 that informed consent was freely given by the subject.

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

If any new information that could influence the subject's decision to stay in the study becomes available, this information will be transmitted to the subject 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 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 the Sponsor (or its representative) from Regulatory Authorities and members of the IRB/IEC may inspect medical records and Case Report Forms for verification of the accuracy of data. These groups are obliged to respect medical confidentiality 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 (or Pediatrician)

If the subject agrees, the Investigator may inform the subject's regular physician of his/her participation in the study.

15 STUDY MANAGEMENT AND ADMINISTRATION

15.1 Monitoring

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a 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 the Sponsor 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 the sponsor 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.

If the monitoring and/or auditing process identifies serious and/or persistent non-compliance by an Investigator/Institution, the Sponsor may terminate the Investigator's/Institution's participation in the study.

15.2 Direct Access to Source Data/Documents

The Investigator(s)/Institution(s) will permit study-related monitoring, audits by or on behalf of the sponsor, 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, etc. Source documents should be kept in a secure, limited access area.

Original laboratory results, ECG tracing and reports, DRC, PRO booklets, etc., will be inserted in the CRF and are also to be 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 investigation product(s), the minimum requirements for source documents used in clinical studies are that they should contain the identity of the subject and study related identifiers (such as treatment numbers, 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 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 source documents verification (SDV) according to the SDV plan prepared for the study.

15.3 Audit and Inspection

The Investigator will permit study-related audits by auditors mandated by the Sponsor and inspections by domestic or foreign regulatory authorities, after reasonable notice. The purposes of an audit or inspection is 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 the Sponsor.

15.4 Case Report Forms (CRF)

Data reflecting participant experience with the drug(s) under investigation will be reported to the Sponsor. These data will be recorded on the CRF. The CRF is essentially a data entry form and may not routinely constitute the original (or source) medical record. CRFs 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 as indicated.

The Investigator's or Principal 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:

- Draw a single line through the incorrect entry.
- Enter the correct data, explain the correction (if necessary), date and initial the change. 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).

The Sponsor cannot interpret a blank answer as "NONE" or "N/A"; therefore, all fields must be completed. If the data are not available, a straight line should be drawn through all applicable fields.

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 must submit to the Sponsor or its representatives a completed CRF for each participant exposed to the investigational product.

All supportive documentation submitted to the Sponsor in addition to the CRF, such as laboratory results or hospitalization records, must be clearly identified with the study number, subject's number, subject's initials and visit number where relevant; any personal information, including the subject's name, must be removed or rendered illegible to preserve individual confidentiality. All original laboratory reports will remain at the study site. Copies of the reports will be placed in the CRF binder (where directed) and forwarded to the sponsor.

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

Any significant 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 and/or auditing by the Sponsor or its designee.

15.7 Data Handling

The Sponsor will be responsible for data processing.

CRF data will be entered in a validated electronic database using a Clinical Data Management System (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. 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 the sponsor or its representatives while maintaining original source documents.
- Data clarification and/or resolution.
- Accountability, reconciliation and arrangements for used and unused study drugs.
- Review of site study records for completeness.
- 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.

15.8.1 Termination of Study by Sponsor

In addition, the Sponsor 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 recurrent non-compliance with respect to quality or quantity.

If the study is prematurely terminated or suspended, the Sponsor 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 study drugs and other material in accordance with the Sponsor procedures for the study.

15.9 Clinical Study Report

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

15.10 Insurance and Liability

The Sponsor 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. Information as to insurance policies held by the Sponsor can be made available to the Investigator and to the IEC/IRB upon request.

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 records 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 the sponsor (ICH-GCP Guideline-Section 4.9.5). The Investigator will contact the Sponsor 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 the Sponsor 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 log of appropriately qualified persons to whom he/she has delegated significant study-related duties ("Delegation of Authority" document with name, function, signature, initials, and dates of participation in the study conduct and type of tasks delegated). The list should be kept up to date.

15.13 Curriculum Vitae (CV)

The Investigators should supply their updated CV (English translation), dated and signed, together with a list of their collaborators responsible for the practical conduct of the study. These collaborators should also provide a recent English version of their CV, dated and signed.

Where applicable, a signed and dated FDA Form 1572 (in Canada, a Qualified Investigator Undertaking Form must also be provided) is 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 from each clinical site for every Investigator and Sub-Investigator participating in the study. 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 after study completion/end of 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 the Sponsor to secure compliance. Continued non-compliance may result in the termination of the participants' involvement in the study.

15.16 Publication

Subject to the provisions of the publication article of the agreement with the Investigator or his/her legal representative, the Sponsor will be responsible for the publication of the results of this study. The site shall not publish or present any research findings resulting from the Study or any scientific work with respect to Sponsor's drug or its development, without the Sponsor's prior written approval of the content of the presentation, manuscript or other materials prepared for publication. The Sponsor will respond to requests for presentation or publication in a timely manner and will not unreasonably withhold authorization.

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17 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 Good Clinical Practice.

[redacted]