1. TITLE

An open-label, multi-center, follow-up trial to evaluate long-term safety and efficacy of brivaracetam (ucb 34714) 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 SA
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Brivaracetam - EudraCT Number: 2004 - 002140-10
IND Number: 75,898

General Substantial Amendment 1 approved 1st April 2005: limitation of the maximal dose to 150 mg/day.
General Non-Substantial Amendment 2 approved 20th May 2005: clarification of several sections of the protocol
Country Specific - Germany- Substantial Amendment 3 approved 30th May 2005: only subjects aged 18 years or more can be included
Country Specific - The Netherlands – Substantial Amendment 4 approved 2nd December 2005: only subjects aged 18 years or more can be included
General Substantial Amendment 5 approved 07th April 2006: compliance with Central EC and Sponsor requirements. Clarification of several sections of the protocol
Specific Substantial Amendment 6 approved 05th May 2006: specifications for subjects with ULD
General Substantial Amendment 7 approved 02nd February 2007: specifications for subjects with POS
General Substantial Amendment 8 approved 01st June 2007: specifications for subjects with POS
Specific Substantial Amendment 9 approved 01st June 2007: specifications for subjects with ULD
Specific Substantial Amendment 10 approved 26th October 2007: specifications for subjects with ULD
Country Specific – Austria – Amendment 11/C3 approved 20-Nov-2007: addition of a monthly urine pregnancy test in female subjects of childbearing potential
Country Specific – France – Amendment 12/C4 approved 11-Feb-2008: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug
Country Specific – Norway – Amendment 13/C5 approved 13-Mar-08: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug and only subjects aged 18 years or more can be included
Country Specific – Spain – Amendment 14/C6 approved 04-Apr-08: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug
Site Specific – Site # [redacted] – Amendment 15/S1 approved 04-Apr-08: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug
Country Specific – Turkey – Amendment 16/C7 approved 04-Apr-08: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug

Site Specific – Site # [redacted] – Amendment 17/S2 approved 04-Apr-08: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug
This amendment applies to all sites (with Partial Onset Seizures subjects) participating in the study
Specific Substantial Amendment 18 approved 04-April-2008: clarification of several sections of the protocol and FDA warning for suicidality and suicidal thoughts for subjects with POS
Site Specific – Site # [redacted] – Amendment 19/S3 approved 29-May-2008: subjects are not allowed to convert to brivaracetam monotherapy in case of excellent efficacy and tolerability of the study drug
Country Specific – France – Amendment 20/C8 approved 09-Jun-2008: subjects are not allowed to enter the study if they are sexually inactive with childbearing potential
Country Specific – Czech Republic – Amendment 21/C9 approved 21-Jan-09: study entry of the N01258 subjects allowed
Country Specific – Germany – Amendment 22/C10 approved 21-Jan-09: study entry of the N01258 subjects allowed
Country Specific – Poland – Amendment 23/C11 approved 21-Jan-09: study entry of the N01258 subjects allowed
Specific Substantial Amendment 24 dated 03 Jan 2011: clarification of several sections of the Integrated Protocol Amendment 18
Specific Substantial Amendment 25 dated 03 Jan 2011: clarification of several sections of the Integrated Protocol Amendment 10
Integrated Substantial Amendment 25 dated 03 Jan 2011 includes the changes to the previous Integrated Amendment 10 and to the Integrated Amendment 18 and applies to all subjects enrolled in N01125.
Integrated Substantial Amendment 26 dated 25 Oct 2011: addition of the suicidality assessment and the requirements per the FDA Final Rule and update of the study variables
Integrated Substantial Amendment 27 dated 12 Mar 2015: updated contact information, addition of procedures for subjects enrolling from another study (N01315), deletion of outdated exposure numbers, addition of language allowing all subjects to enroll into a managed access program (or similar), updated protocol adherence language, added Sponsor declaration page

Confidential Material

"The information contained in this document is strictly confidential. It is disclosed to you as a (potential) Investigator or (potential) consultant. Acceptance of this document constitutes your agreement that the information contained herein will not be disclosed or in anyway communicated to any third party without prior written approval of the Sponsor (or it's representative(s) of the clinical study described therein except – to the extent necessary – to your staff, to members of appropriate review committee(s) and/or to persons to whom the investigational product may be administered or to their legal representative(s) to obtain their informed consent."

Principal Investigator

"By my signature below, I acknowledge that I have read the protocol RPCE03D0801 Integrated Amendment 27 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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Investigator(s)
The complete and updated list of Investigators is maintained in the Trial Master File (TMF) at UCB.

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3.1 List of Abbreviations

AE	Adverse Event
AED(s)	Antiepileptic Drug(s)
ALAT/SGPT	Alanine Aminotransferase/Serum Glutamic Pyruvic Transaminase
ALP	Alkaline Phosphatase
ASAT/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
AMD(s)	Antimyoclonic Drug(s)
AUC	Area Under the Curve
$AUC_{(o-t)}$	Area Under the Curve from time 0 to infinity
b.i.d.	Twice Daily
BRV	Brivaracetam
CBZ	Carbamazepine
CBZE	Carbamazepine-10,11-epoxide
CDMS	Clinical Data Management System
cDNA	Copy-deoxyribonucleic Acid
CLB	Clobazam
C_{max}	Highest Drug Concentration Observed in Plasma following Administration of an Extravascular Dose (= peak plasma level)
CNS	Central Nervous 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
CTA	Clinical Trial Application
CTM	Clinical Trial Manager
CV	Curriculum Vitae
CZP	Clonazepam
dl	Deciliter
DRC	Daily Record Card
DTP	Down-titration Phone Call
ECG	Electrocardiogram
ED_{50}	Effective Dose
EDV	Early Discontinuation Visit
EEG	Electroencephalogram
EQ-5D	EuroQol 5 Dimensions Questionnaire
ESM	Ethosuximide
EV	Entry Visit
FBM	Felbamate
FEV	Full Evaluation Visit
FSH	Follicle-stimulating Hormone
GAERS	Genetic Absence Epilepsy Rats from Strasbourg
GBP	Gabapentin

GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma-glutamyltranspeptidase
GMP	Good Manufacturing Practices
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act Authorization
HRQOL	Health-related Quality of Life
β-hCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-to-treat
ITT PGS	Intention-to-treat Population for Primary Generalized Epilepsy
ITT POS	Intention-to-treat Population for Localization Related Epilepsy
kg	Kilogram
L	Liter
LBS	Levetiracetam Binding Site
LEV	Levetiracetam
LH	Luteinizing Hormone
LTFU	Long-term Follow-up
LTG	Lamotrigine
M	Month
MAD	Minimum Active Dose
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
µM	Micromole
ms	Millisecond
Na	Natrium
NOAEL	No-observed-adverse-effect Level
NOEL	No-observed-effect Level
OC	Oral Contraceptive
OXC	Oxcarbazepine
PB	Phenobarbital

PBO	Placebo
PGB	Pregabalin
PGS	Primary Generalized Seizures
PHT	Phenytoin
PK	Pharmacokinetics
POS	Partial Onset Seizures
PP	Per Protocol
PRO	Patient Reported Outcomes
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Questionnaire
QTc	QT Interval Corrected
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Source Documents or Standard Deviation
SDR	Safety Data Review
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV2A	Synaptic Vesicle Protein 2A
t ½	Half-life
TEAE	Treatment-emergent adverse event
TGB	Tiagabine
TMF	Trial Master File
TPM	Topiramate
UDP-GT	Uridine 5'-diphosphate Glucuronyl Transferase
ULD	Unverricht-Lundborg Disease
V	Visit
VGB	Vigabatrin
VPA	Valproate
W	Week
WBC	White Blood Cell
WHO	World Health Organization
YEV	Yearly Evaluation Visit
ZNS	Zonisamide

4. PROTOCOL SUMMARY

Study Number: N01125

Title of the study: An open-label, multi-center, follow-up trial to evaluate long-term safety and efficacy of brivaracetam (ucb 34714) 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.

Study Objectives
For all subjects:

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

For subjects with partial onset seizures (POS)/primary generalized seizures (PGS):

- To evaluate the maintenance of efficacy over time of brivaracetam
- To explore direct 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 the effects of BRV on the subject's Health-related Quality of Life, anxiety, and depression for the first 2 years
- To explore any change in the subject's socio-professional status for the first 2 years

This open-label long-term follow-up (LTFU) study will give subjects suffering from epilepsy, for whom the Investigator believes a reasonable benefit from the long-term administration may be expected, the opportunity to access adjunctive brivaracetam treatment. Conversion to monotherapy is not permitted anymore, however, subjects already on monotherapy are allowed to continue BRV monotherapy. The access to the study will be limited to the subjects having completed a previous brivaracetam study as listed in Section 5.6.

Methodology:
Multi-center, open-label, single arm study.

The individual starting dose of each subject will be the one recommended at the end of the previous study. Dose adjustment of study drug and/or concomitant antiepileptic drugs (AEDs) or antimyoclonic drug (AMDs) is allowed at any time during the study if seizure control is insufficient, or in case of safety or tolerability issue.

Study Type/Phase:
Therapeutic study/long-term follow-up.

Diagnosis and Main Criteria for Inclusion:

- Male/female subjects from 16 years (where legally permitted and ethically accepted) or 18 years onwards suffering from epilepsy and having completed a previous study with brivaracetam as adjunctive treatment, which allowed access to this study.
- Subjects for whom the Investigator believes a reasonable benefit from long-term administration of brivaracetam may be expected.

Study Period (years):
This study will run throughout the duration of the clinical development period of brivaracetam, 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 a managed access program, named patient program, compassionate use program, or similar type of access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines, or until brivaracetam development is stopped by the Sponsor.

Number of Subjects (planned):
500-1000 subjects, based upon the assumption that 90% of subjects having completed a previous study with brivaracetam as adjunctive treatment in epilepsy will roll over into the present study.

Number of Sites (planned):
As many sites as required and estimated between 150-200 sites.

Countries (planned):
This will be a worldwide protocol.

Investigational Product (dose, mode of administration):
brivaracetam - oral tablets containing 10 mg or 25 mg of brivaracetam.

Reference Product: Not applicable

Study Duration per Subject:
For each subject, the study will last from study entry until either regulatory approval of brivaracetam has been granted by any Health Authority in an indication of adjunctive treatment of partial onset seizures; or until the Sponsor decides to close the study; until a managed access program, named patient program, compassionate use program, or similar type of access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines, or until the investigational product development is stopped by the Sponsor.

Safety Variables

Note: Assessments specified as performed within the first 2 years of the Evaluation Period are not applicable to subjects coming from N01315.

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

- Other safety variables
  - Laboratory tests (blood chemistry, hematology, urinalysis)
  - Vital signs (systolic blood pressure, diastolic blood pressure, 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

Efficacy variables

Note: Assessments specified as performed within the first 2 years of the Evaluation Period are not applicable to subjects coming from N01315.

- Secondary efficacy variables

  For subjects with focal-onset epilepsy:
  - Partial onset seizure (type I) frequency per 28 days during the Evaluation Period.
  - Percent reduction in POS (type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period.
  - 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.

  No secondary efficacy variables are defined for subjects with generalized epilepsy, subjects with Unverricht-Lundborg Disease (ULD), or subjects coming from N01315.

- 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.

No other efficacy variables are defined for subjects with ULD or coming from N01315.

Pharmacoeconomic variables

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

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

No pharmacoeconomic variables are defined for subjects with ULD or for subjects coming from N01315.

The periods considered are:

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

Statistical Methods:
All safety and efficacy variables will be analyzed using descriptive statistical methods.

4.1 Schedule of Assessments

Table 4:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)	Down-Titration Phone Call (DTP)[j]	Drug-free Period Final Visit (FV)	Reference to Section
Assessments									
Written Informed Consent	X								10.2.1
Clinical Trial Subject Card dispensing	X								10.5
Verification incl./excl. criteria	X								8.1/8.2
Demographic data	X								10.2.2
Childbearing potential	X								10.2.3
Medical and procedures history	(X)[a]								10.2.4
Epilepsy history/disease history[h]	(X)[a]								10.2.5
AED/AMD history[h]	(X)[a]								10.2.6
Vital signs	(X)[a]	X	X	X		X		X	10.2.7
Body weight and height[c]	X	X		X		X		X	10.2.8
Physical examination	(X)[a]	X		X		X		X	10.2.9
Neurological examination	(X)[a]	X		X		X		X	10.2.10
ECG[d]	(X)[a]			X		X		X	10.2.11
Daily record card dispense	X	X	X	X		X			10.2.12
Daily record card retrieval		X	X	X		X		X	10.2.12
Recording of seizures	(X)[a]	X	X	X		X		X	10.2.12
QOLIE-31-P[f] [k]		X[i]	M3[e]	X		X			10.2.14
HADS[f] [i] [k]		X		X		X			10.2.15

Table 4:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)	Down-Titration Phone Call (DTP)[j]	Drug-free Period Final Visit (FV)	Reference to Section
Assessments									
Laboratory assessments[g]	(X)[a]	X		X		X		X	10.2.16
Recording of Adverse Events	X[b]	X	X	X	X	X	X	X	10.2.17
C-SSRS[l]		X	X	X	X[m]	X		X	10.2.18
Medical procedures	X[b]	X	X	X	X	X		X	10.2.19
Healthcare provider consultation not foreseen by protocol[f]		X	X	X		X		X	10.2.20
Workdays and schooldays lost due to inability to perform an usual activity and days with caregiver's help (excluding paid work)[f]		X	X	X		X		X	10.2.12
Hospital stay[f]		X	X	X		X		X	10.2.21
EQ-5D Questionnaire[f] [n]		X		X		X			10.2.23
Socio-professional Data[f] [o]				X		X			10.2.24
Concomitant AED/AMD[h]	X[b]	X	X	X	X	X		X	9.2
Concomitant non AED/AMD[h]	X[b]	X	X	X	X	X		X	9.2
Drug dispensing	X	X	X	X	(X)	X			9.1.1
Drug return/accountability		X	X	X		X		X	9.1.6
Down-titration						X			9.1.1.1
End of study status								X[p]	10.2.25
Clinical Trial Patient Card return								X	10.5

Table 4:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)	Down-Titration Phone Call (DTP)[j]	Drug-free Period Final Visit (FV)	Reference to Section
Assessments									

AED=antiepileptic drug; AMD=antimyoclonic 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; IEC=Independent Ethics Committee; IRB=Institutional Review Board; MEV=Minimal Evaluation Visit; QOLIE=Patient Weighted Quality of Life in Epilepsy Questionnaire; ULD=Unverricht-Lundborg disease; YEV=Yearly Evaluation Visit

(a) The following data (in parentheses) will be transferred electronically from the previous study and should not be recorded in the CRF:
From the First Visit: General Medical and Procedure history, epilepsy history, disease history (for ULD subjects only), AED history and AMD history (for ULD subjects only).
From the last Evaluation Visit: vital signs, physical and neurological examinations, ECG, recording of seizures, laboratory assessment.

(b) Ongoing AE, procedures and medications at the end of previous study have to be recopied into the N01125 CRF appropriate sections (except subjects from N01315).

(c) Height will only be recorded at Visit 1 (EV). Height will also be measured at each YEV and FV for subject still in growing period.

(d) If an ECG has not been performed within the year, an ECG has to be scheduled once a year at the YEV. As well, an ECG shall be performed at the EDV and at the FV (if applicable). An ECG is mandatory at FV except if FV follows an EDV where ECG results were normal.

(e) For subjects coming from study N01114 and for ULD subjects.

(f) Procedures only performed during the first 2 years of subject participation in the study (eg. till last scheduled visit (YEV-Y3) or EDV/FV in case the subject discontinues participation within the first 2 years).

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

(h) Disease history, AMD history, concomitant AMD and concomitant nonAMD are collected only for ULD subjects.

(i) Procedure not to be performed for ULD or N01315 subjects.

(j) Down-Titration Phone call at the end of the Down-Titration Period is mandatory for all subjects in case the subjects discontinue from more than 20 mg/day brivaracetam. This phone call will also replace the previous Down-Titration Visit for ULD subjects.

(k) QOLIE-31-P and HADS (not for ULD and N01315 subjects) are to be completed at the beginning of the visit by all subjects who are not mentally impaired.

(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 26, all subjects had completed their EV. Thus, the C-SSRS was not assessed for any subjects at their EV.

(m) The C-SSRS will be done at the AV in case the AV is conducted for safety and efficacy reasons.

Table 4:1 Study Flowchart

	Entry Visit (EV)	Full Evaluation Visit (FEV)	Minimal Evaluation Visit (MEV)	Yearly Evaluation Visit (YEV)	Additional Visit (AV)	Early Discontinuation Visit (EDV)	Down-Titration Phone Call (DTP)[j]	Drug-free Period Final Visit (FV)	Reference to Section
Assessments									

[n] EQ-5D questionnaire is to be completed only by subjects coming from N01252 and N01254, and if not mentally impaired.

[o] Socio-professional status is to be completed only by subjects coming from N01252 and N01254.

[p] 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).

4.2 Schematic Diagram

For subjects coming from the therapeutic exploratory study (N01114):

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

For subjects coming from confirmatory studies (N01252 and N01254):

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

For subjects coming from ULD confirmatory studies (N01187 and N01236):

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

For subjects coming from long-term follow up study N01315:

- Subjects will perform their Last Visit in N01315 and perform at the same time their First Visit in N01125. They will follow the schedule of 1 visit/3 months: 1 Full Evaluation Visit alternating with 1 Minimal Evaluation Visit. Yearly Evaluation Visit will be performed in replacement of the first Full Evaluation Visit of each year.

Table 4:2 Schematic Diagram

Subjects coming from Exploratory Studies (N01114)			**Subjects coming from Confirmatory Studies (N01252, N01254)**		
Month	**Visit**	**Type of Visit**	**Month**	**Visit**	**Type of Visit**
1st year Follow-up			**1st year Follow-up**		
MO	V1	Entry Visit	MO	V1	Entry Visit
M1	V2	MEV	M1	V2	MEV
M2	V3	FEV	M2	V3	FEV
M3	V4	MEV	M3	V4	MEV
M4	V5	FEV	M4		
M5	V6	MEV	M5		
M6	V7	FEV	M6	V5	FEV
M7			M7		
M8			M8		
M9	V8	FEV	M9	V6	MEV
M10			M10		
M11			M11		
2nd and subsequent years Follow-up			**2nd and subsequent years Follow-up**		
M12	V9	YEV	M12	V7	YEV
M15	V10	MEV	M15	V8	MEV
M18	V11	FEV	M18	V9	FEV
M21	V12	MEV	M21	V10	MEV

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

Subjects coming from ULD Confirmatory Studies (N01187, N01236)		
Month	**Visit**	**Type of Visit**
1st year Follow-up		
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	MEV
M18	V9	FEV
M21	V10	MEV
...	...	...

FEV=Full Evaluation Visit; MEV=Minimal Evaluation Visit; M=month; ULD=Unverricht-Lundborg disease; V=Visit; YEV=Yearly Evaluation Visit

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 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 one 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 study drug-free period and subsequently the Final Visit will occur.

At the time of study termination by the Sponsor (as defined in Section 7.4), subjects will discontinue the study drug following the above described down titration process or will be converted without titration to commercial BRV where available, alternatively subjects may 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 requirements in addition to legal and regulatory guidelines.

5. BACKGROUND INFORMATION

5.1 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[1, 2, 3, 4]. The prevalence of epilepsy is around 1%. The annual incidence in developed countries is approximately 50 to 70 cases per 100,000. In developing countries, the figure is higher due to more limited obstetric services and the greater likelihood of cerebral infection and trauma. The incidence varies greatly with age, with high rates occurring in childhood, falling to low levels in early adult life, but with a second peak in those aged over 65 years. In many people, particularly children, the condition may remit, although a significant proportion will have epilepsy lifelong. The disease duration is often determined by the underlying cause. Sudden unexpected death, a complication of great concern, occurs in 1 to 5 per 1000 patient years, particularly if the seizure disorder remains uncontrolled. The treatment for epilepsy remains difficult, and there is an ongoing medical need for new antiepileptic drugs (AEDs). For a considerable proportion of patients, seizure freedom can still not be reached with currently available AEDs[5, 6].

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[7] ILAE [http://www.ilae-epilepsy.org]). The availability of these modern techniques, like long-term video electroencephalograms (EEG) and high-resolution magnetic resonance imaging (MRI), providing much more precise knowledge in regard to seizure type classifications and epileptic syndromes, led some epilepsy groups and scientists towards introducing competing classification systems (like the Cleveland Clinic Epilepsy Classification) and even debating how useful the currently used ILAE classification system is at all[8].

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[9].

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[10] (Commission on Classification and Terminology of the ILAE, 1981).

Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAE-publication[11] (Commission on Classification and Terminology of the ILAE, 1989).

5.2 Background information regarding product

Brivaracetam is a chemical relative of the AED levetiracetam (LEV) (Keppra®). Like LEV, brivaracetam displays a high and selective interaction with a novel brain-specific binding site SV2A (synaptic vesicle protein 2A). However, the binding affinity of brivaracetam for SV2A is approximately 10-fold higher. This binding site appears to be the major target for its pharmacological activity. Unlike LEV, brivaracetam also reduces voltage-dependent sodium currents. Brivaracetam also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid - and glycine-induced currents. Brivaracetam is extensively metabolized, but seizure protection appears to be associated with the parent compound. Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of brivaracetam absorption is not affected by food. The pharmacokinetics (PK) is 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 brivaracetam is approximately 8 hours in young healthy male adults. The main metabolic pathway of brivaracetam 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 brivaracetam. Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, with less than 9% as unchanged brivaracetam, 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 brivaracetam 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 brivaracetam 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 and topiramate. Brivaracetam plasma concentration is not increased by gemfibrozil, a selective CYP2C8/9 inhibitor but is increased in a nonclinically relevant manner in Japanese subjects possessing defective CYP2C19 mutations. Brivaracetam clearance is doubled by rifampicin, a potent CYP inducer.

Trough levels of concomitant AEDs were monitored in all efficacy studies. No significant change from Baseline nor dose-related trend was observed for the plasma concentrations of: carbamazepine, lamotrigine, LEV, oxcarbazepine metabolite, phenobarbital, phenytoin, topiramate, valproate, zonisamide. Carbamazepine epoxide was significantly increased from Baseline at all brivaracetam doses greater than 20 mg/day, nearly reaching the upper limit of normal (3.0 µg/mL) at brivaracetam doses of 100 and 150 mg/day.

5.3 Efficacy with brivaracetam in fixed-dose Phase II/III studies in POS

Following completion of the Phase II studies (N01114[12] and N01193[13]), clinical results supported further development of brivaracetam for the adjunctive treatment of POS. Two adequate and well-controlled fixed-dose studies (N01252[14] and N01253[15]) were conducted to assess brivaracetam across a dose range of 5 to 100 mg/day.

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

5.4 Safety with brivaracetam

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

5.5 Efficacy and safety in subjects with Unverricht-Lundborg disease

Two Phase III studies (N01187[16] and N01236[17]) were conducted to evaluate the efficacy and safety of brivaracetam (5, 50, and 150 mg/day) used as adjunctive treatment in adult subjects with genetically ascertained ULD. In both studies, primary efficacy endpoints failed to reach statistical significance. In N01187, the most frequently reported TEAEs were headache, somnolence, and dizziness. In N01236, the most frequently reported TEAEs were headache, myoclonus, and somnolence. There were no deaths or clinically relevant changes from Baseline observed for any vital sign parameters. Results indicate that in this population of ULD subjects, brivaracetam administered for 16 weeks was well tolerated.

For additional details on safety and efficacy of BRV, please refer to the Investigator's Brochure[18].

5.6 Study Rationale

The Sponsor wishes to develop brivaracetam as an antiepileptic treatment in subjects 16 years and older suffering from epilepsy. This N01125 study will give subjects who have participated in a previous brivaracetam adjunctive treatment study in epilepsy, the opportunity to access adjunctive brivaracetam 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 seizure (subjects coming from N01114, N01252, N01254[19], and N01315), while a minority will present with generalized epilepsy (subjects coming from N01254 and N01315). The study will explore the long-term safety and efficacy of brivaracetam in such a population.

It is to be noted that subjects suffering from Unverricht-Lundborg disease (ULD) and having participated in a previous UCB brivaracetam study (N01187 or N01236) are also allowed to participate in N01125.

5.6.1 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 brivaracetam studies (eg, N01358 and N01379). According to available data, 200 mg/day doses have been well tolerated.

5.6.2 Subjects Population

5.6.2.1 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 AEDs seems to be comparable[20].

Depending on country-specific regulations, those subjects may be considered as adolescents or adults[21]. 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.

5.6.3 Duration of Treatment

For each subject, the study will run throughout the duration of the clinical development period of brivaracetam, 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 a managed access program, named patient program, compassionate use program, or similar type of access program established as allowed per country-specific requirements in addition to legal and regulatory guidelines, or until brivaracetam 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][22].
- The principles that have their origin in the Declaration of Helsinki.
- Code of Federal Regulations on Good Clinical Practice Title 21 Parts 50, 54, 56, 312, and 314.
- All applicable local laws and regulations.

It is planned that approximately 30 sites enrolling ULD subjects will be involved in the US, Canada, Finland, France, Italy, The Netherlands, Sweden, Tunisia, and India. For the sites having participated in the previous ULD study N01236, this study will be conducted under the Investigational New Drug (IND) regulation in the US, in Finland, Tunisia, and in France. For the sites having participated in the previous ULD study N01187, this study will not be conducted under IND/CTA. This study will not be conducted under the IND for all sites that enrolled only POS/PGS subjects. For the sites having participated in the study N01315 conducted under IND regulation, this study will not be conducted under IND/CTA as N01315 enrolled only POS subjects.

6. STUDY OBJECTIVES AND PURPOSE

This open long-term follow-up study will give subjects suffering from epilepsy, for whom the Investigator believes a reasonable benefit from the long-term administration may be expected, the opportunity to access adjunctive brivaracetam treatment. Conversion to monotherapy is not permitted anymore, however, subjects already on monotherapy are allowed to continue BRV monotherapy. The maximum dose was increased to align with more recent LTFU studies. The access to the study will be limited to the subjects having completed a previous brivaracetam study as listed in Section 5.6.

6.1 Primary Objective

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

6.2 Secondary Objective

- To evaluate the maintenance of efficacy over time of brivaracetam (for POS/PGS subjects)

No efficacy objectives are defined for ULD subjects or subjects coming from N01315.

6.3 Exploratory Objectives

Exploratory objectives for POS/PGS subjects:

- To explore direct 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 the effects of BRV on the subject's Health-related Quality of Life, anxiety, and depression for the first 2 years
- To explore any change in the subject's socio-professional status for the first 2 years

No exploratory objectives are defined for ULD or N01315 subjects.

7. STUDY DESIGN

7.1 Type/Design

This is a therapeutic long-term follow-up, multinational, multi-center, noncomparative, open-label and single arm study.

This long-term follow-up study will run throughout the duration of the clinical development period of brivaracetam, and will thus include therapeutic exploratory studies in the early stage of development as well as therapeutic confirmatory studies, in the later stage of the development. For this reason, the study design and in particular the frequency of study visits is adapted to the 3 types of study, as described below:

For subjects coming from the therapeutic exploratory study (N01114):

- First year:
  First 6 months: 1 visit/month: 1 FEV alternately with 1 MEV.
  Next 6 months: 1 visit/3months: 2 FEV (at V7 and V8).
- Second and subsequent years:
  1 visit/3months: 1 FEV alternately with 1 MEV.
  Yearly Evaluation Visit will be performed in replacement of the first FEV of each year.

For subjects coming from confirmatory studies (N01252 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.
  Yearly Evaluation Visit will be performed in replacement of the first FEV of each year.

For subjects coming from ULD confirmatory studies (N01187 and N01236):

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

For subjects coming from long-term follow up study (N01315):

- Subjects will perform their Last Visit in N01315 and perform at the same time their First Visit in N01125. They will follow the schedule of 1 visit/3 months: 1 Full Evaluation Visit alternating with 1 Minimal Evaluation Visit. Yearly Evaluation Visit will be performed in replacement of the first Full Evaluation Visit of each year.

7.2 Subjects/Sites Numbers

A 90% switch over rate is estimated as compared to the number of subjects completing the previous brivaracetam studies.
Approximately 500-1000 subjects may enter the study.

7.3 Measures to Minimize/Avoid Bias

7.3.1 Randomization

Not applicable.

7.3.2 Blinding

Open-label.

7.4 Study Duration

This study will run throughout the duration of the clinical development period of brivaracetam, 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 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 brivaracetam development is stopped by the Sponsor.

7.5 End of Study

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

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

8.1 Subject Inclusion Criteria

- An IEC/IRB approved written informed consent signed and dated by the subject or legally acceptable representative(s). The consent form or a specific assent form will be signed and dated by minors, according to country-specific regulations.
- Male/female subjects from 16 years or older. Subjects under 18 years may only be included where legally permitted and ethically accepted.

- Subjects with POS/PGS: inpatients or outpatients with epilepsy who participated in previous brivaracetam studies / programs which allow access to the present study. Subjects with ULD: inpatients or outpatients with epilepsy who were treated with brivaracetam in previous studies / programs which allow access to the present study.
- Subjects for whom the Investigator believes a reasonable benefit from the long-term administration of brivaracetam may be expected.
- Female subjects with childbearing potential:
  - POS/PGS subjects: 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 participation (Intra Uterine Device; diaphragm with spermicide; male or female condom with spermicide; oral hormonal contraceptive; non-oral hormonal contraceptive medication; bilateral tubal ligation; monogamous relationship with vasectomized partner). In particular, oral or depot contraceptive treatment with at least 30 µg [or 50 µg if associated with carbamazepine (CBZ) or other strong enzyme inducing drugs] ethinylestradiol per intake must be used in conjunction with a barrier method. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. Sexual inactivity might be accepted on a case-by-case basis according to the judgment of the Investigator.
  - ULD subjects: Female ULD subjects without childbearing potential (premenarcheal, postmenopausal for at least 2 years, bilateral oophorectomy or tubal ligation, complete hysterectomy) are eligible. Female subjects with childbearing potential are eligible if they use a medically accepted contraceptive method. Oral or depot contraceptive treatment with at least 30 µg [or 50 µg ethinylestradiol per intake if associated with carbamazepine (or other strong enzyme inducers e.g. phenobarbital, primidone, oxcarbazepine)] must be used in conjunction with a barrier method. Monogamous relationship with vasectomized partner or double-barrier contraception are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. 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 (eg, able to understand and complete diaries and questionnaires), visit schedule or medication intake according to the judgment of the Investigator.

8.2 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 visit schedule or medication intake in previous brivaracetam study.
- Participation in any clinical study of another investigational 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 eligibility, he/she should consult the Sponsor's Clinical Study Physician or representative for clarification.

8.3 Subject Withdrawal Criteria

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 Final Visits. 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 until a study drug-free state is reached. After a period of free of study medication, the subject will attend the Final Visit.

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

The Sponsor could decide to discontinue or prematurely terminate the study for reasons related to safety and/or efficacy of the Investigational Product or, decide to stop the development of brivaracetam.

8.3.1 Withdrawal Criteria

- Withdrawal for safety reasons by the Investigator.
- Subject and/or Investigator does not think that the investigational drug is effective.
- Lost to follow-up.
- Withdrawal of consent by the subject for any reason, at any time.
- Other reason that has to be specified in the CRF.

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

- Subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
- Subject had active suicidal ideation prior to study entry or since study start as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.
- Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

8.3.2 Subject Replacement Policy

Not applicable.

9. TREATMENT OF SUBJECT (INVESTIGATIONAL PRODUCTS AND CONCOMITANT MEDICATIONS)

9.1 Study Investigational Products

9.1.1 Description of Investigational Products

The investigational product (tablets containing 10 mg or 25 mg of brivaracetam) 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 center will be adapted to the recruitment capacity of that center and to the expiry date of the investigational product.

9.1.1.1 Dosing Schedule

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

The individual starting dose of each subject will be the one recommended at the end of the previous study.

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

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

At each visit, the Investigator will evaluate, as closely as possible, the supplies needed by the subject in terms of number of containers (200 tablets per container) 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.

In case the subject will not continue with the study drug, 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 two weeks and a maximum of four weeks and subsequently the Final Visit will occur.

9.1.2 Packaging

Tablets of brivaracetam (10 mg or 25 mg) will be packaged in containers of 200 tablets. Containers of 80 tablets have been removed. On request, 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 included on how to take the drug and that an excess of drug is present in the investigational product container.

9.1.3 Labeling

Each type of container will be distinguished, per dosage, by colored labels.
The label consists of two 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.

Clinical Drug Supplies will be labeled in accordance with the current ICH Guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any locally required statements.
The label will be adapted to local regulatory requirements and to the size of the investigational product package, and translated as appropriate.

Subject number, subject initials, dispensation date and name of Investigator will be added manually by the Investigator before dispensing. Dosage instructions will be specified in the dispensing card.

9.1.4 Storage Requirements

Investigational product packages should be stored in a secured limited access area and maintained at controlled temperature (as specified on the label of the investigational product packages). A recording of the 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.

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 package label of study medication.

The Investigator or the hospital pharmacist is responsible for the appropriate storage of investigational product packages at the research site.

The Investigator will instruct the subject/legally acceptable representative to store the medication at controlled temperature (as specified on the label) in a secure place out of the reach of children.

9.1.5 Monitoring of Subject Compliance

Containers of study drug will be supplied to each subject at each Visit. Subjects will be instructed to ingest the study drug in the morning and in the evening (approximately 12 hours between doses).

The Investigator will instruct the subject to bring back at each visit, the original containers (even empty) dispensed at the previous visit and containing all the remaining tablets of the study medication. Drug reconciliation must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regime. This information will be documented on the drug accountability form (see also Section 9.1.6).

The number of tablets returned must be recorded in the CRF. Compliance with study medication is defined as investigational product consumption by the subject within 80% - 120% of the prescribed dosage.

9.1.6 Investigational Products Accountability

The Sponsor or its representative will supply a drug accountability form, to be kept up-to-date. Study medication disposition records, such as shipping, dispensing and returned drug records, inventory logs, must be kept at the site.

Drug accountability form should include at least:

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

After completion of the study, all used (including empty bottles) and unused investigational product containers must be reconciled and returned (preferably in their original package) to the Sponsor, according to a procedure to be defined at the time.

9.1.7 Maintenance of Study Treatment Randomization Codes and Procedures for Blind Breaking

Not applicable.

9.2 Concomitant Treatments

For any treatment other than the investigational product, 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, the date(s) of administration, and the indication for use.

9.2.1 Permitted Concomitant Treatments (Medications and Therapies)

The Investigator may adapt the AED/AMD drug/dosage for safety or efficacy reasons.

Benzodiazepines taken more than once a week will be considered as AED/AMD.

9.2.2 Not Permitted Concomitant Treatments (Medications and Therapies)

Felbamate and vigabatrin are not permitted for all subjects. Phenytoin is not permitted for ULD subjects.

10. STUDY PROCEDURES

Note: Entry Visit procedures for N01315 subjects were already conducted and will not be repeated in N01125. Assessments specified as performed within the first 2 years of the Evaluation Period are not applicable to subjects coming from N01315.

10.1 Subject Identifier

Each subject will be identified by initials (only letters preferably 4, without spaces or any punctuation signs like coma, slash, hyphen, etc.) and subject number. The subject number will be different from the previous study in which the subject was participating and it includes a newly assigned site number and a sequential enrollment number per site.
At the level of the database, the Master CRF number (from CRFs Yearly Book one) will be used as additional identifier to the subject numbers. Subjects coming from N01315 will retain their current subject numbers.

10.2 Description of Procedures

For N01315 subjects, ongoing procedures will be transferred electronically from the previous study and should not be recorded again in N01125 CRF.

10.2.1 Informed Consent

Before any study-related procedures are performed, an IEC/IRB approved informed consent will be properly executed and documented.

For subjects already ongoing in the study, an IEC approved addendum will also be signed covering the increased risk of suicidality or suicidal thoughts to comply with the warning issued by FDA subsequent to an analysis performed on marketed antiepileptic drugs. Although data from brivaracetam studies were not included in FDA's analysis, this risk cannot be ruled out because brivaracetam belongs to this class of medications.

Where legally acceptable, a Partner Pregnancy Consent Form will be issued in case the partner of a male subject becomes pregnant (Section 12.3.5).

10.2.2 Demography

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

10.2.3 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 a subject's status change. A pregnancy test will be performed as specified in the flow chart (Section 4.1).

10.2.4 General Medical and Procedures History

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

10.2.5 Epilepsy History/Disease History

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

Similarly, a disease history will be recorded for ULD subjects only.

10.2.6 Antiepileptic/Antimyoclonic Medication History

The AED medication history and the AMD medication history (for ULD subjects) will be transferred electronically from first visit of the previous study in which the subject was participating. The AED and AMD being used concurrently at the current dose will be recorded on the concomitant AED/AMD medication page of the CRF.

10.2.7 Vital Signs

At every visit, after five minutes supine or sitting, pulse rate and blood pressure will be obtained, followed by 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.

10.2.8 Body Weight and Height

At Entry Visit, at each Full Evaluation Visit, at each Yearly Evaluation Visit, and at the Final Visit, body weight (subject wearing light clothing without shoes and rounded to the nearest kilogram) will be obtained. Height will be obtained only at the Entry Visit. For a subject still potentially growing, height will also be measured at each Yearly Evaluation visit and Final Visit.

10.2.9 Physical Examination

Physical examination will be performed at every Full Evaluation Visit, Yearly Evaluation Visit, Early Discontinuation Visit and Final Visit. 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. The standard physical examination will include investigation of skin, eyes, ear, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, musculoskeletal system, endocrine, metabolic and nutritional system, blood and blood-forming organs and immune system and optionally genitourinary system.

10.2.10 Neurological Examination

At every Full Evaluation Visit, Yearly Evaluation Visit, Early Discontinuation Visit and Final Visit a standard neurological examination will be performed, consisting of a brief review of cortical functions, cranial nerves, motor function, reflex function, sensory function, gait and stance. 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. Psychiatric and mental status will be reported by recording the presence or absence of psychiatric symptoms, mental impairments and behavioral symptoms.

10.2.11 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: at the Yearly Evaluation Visit, Early Discontinuation Visit and at the 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.

10.2.12 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)

A new DRC designed according to these protocol amendment requirements, to reflect the update of the assessments and to enhance the subjects' compliance will be used by all subjects from the visit following the IEC/IRB approval and after the subject has signed the N01125 Informed Consent.

Due to the nature of their disease, some ULD subjects may be unable or have physical difficulty in writing down their answers. These subjects may be helped by asking the subject's legally acceptable representative/care giver/study nurse/study physician to write down their answers; the helping person should preferably be the same during the course of the study.

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 (except for ULD subjects); 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).

10.2.13 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. Subjects coming from the N01114 will not have to complete the EQ-5D questionnaire and ULD and N01315 subjects will not have to complete the EQ-5D questionnaire and the HADS.

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.

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

10.2.14 Health Related Quality of Life Questionnaire (QOLIE-31-P)

The QOLIE-31-P[23] will be only completed by subjects coming from studies during which Health-related Quality of Life (HRQOL) was a part of the assessment.

The subjects will complete the QOLIE-31-P (Version 2) at Month 3 (for subjects coming from N01114 and ULD subjects only), at every Full Evaluation Visit (for POS and PGS subjects only), at every Yearly Discontinuation Visit for the first 2 years, and at the Early Discontinuation Visit if the Early Discontinuation Visit occurs within the first 2 years. Subjects coming from N01315 will not complete the QOLIE-31-P (Version 2) in this study.

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument[24] that includes seven subscales (seizure worry, overall quality of life, emotional well-being, energy-fatigue, cognitive functioning, medication effects, and social function) and the health status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains seven 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 questionnaire will be completed by the subject, provided he/she is not mentally impaired.

It will be considered as part of the CRF as well as source documentation.

10.2.15 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) will be used to evaluate anxiety and depression/depressed feelings. The HADS will not be assessed in subjects with ULD or from N01315. 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.

10.2.16 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 serum pregnancy tests (if the local urine pregnancy test was positive) will be provided by fax to the Investigator within 72 hours after sample receipt.

Total blood volume drawn for clinical laboratory assessments will be maximum 11 mL/sampling. Subject should preferably be fasting. Study medication intake must not be delayed.

The following laboratory assessments will be conducted:

- Blood chemistry: glucose, urea, creatinine, sodium, potassium, calcium, phosphorus (inorganic), total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase (ASAT/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALAT/SGPT), gamma-glutamyltranspeptidase (GGT), and uric acid.
- The creatinine clearance (Cr Cl) will be calculated by the Cockroft's formula (only at 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, %), other cells (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, haemoglobin casts, uric acid crystals, bihydrate calcium oxalate crystals, monohydrate calcium oxalate crystals, triple phosphate crystals and bacteria) will be conducted.
- Where applicable (women with childbearing potential), a local urine pregnancy test (human chorionic gonadotropin [β-hCG] levels) will be conducted. In case of a positive outcome, a serum pregnancy test will be performed by the central laboratory. If pregnancy is suspected at any time during the study, an interim test should be performed.

Plasma samples to analyze brivaracetam and concomitant AED/AMD plasma concentrations have been collected up to Protocol Amendment 25, dated 03 Jan 2011, but will no longer be obtained.

10.2.17 Adverse Events

At Entry Visit, the Investigator will record all the adverse events that were still ongoing at the end of the previous study. From 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 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. daily record cards) used in the study.

10.2.18 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 4.1).

10.2.19 Medical Procedures

At Entry Visit, the Investigator will record all the medical procedures that were still ongoing at the end of the previous study. From Entry Visit onwards, collection of data on medical procedures (surgery, therapeutic and/or diagnostic, hospitalizations) undertaken during the study will be obtained. ECGs required by protocol will not be recorded on the Medical Procedures page of the CRF, but on the ECG module.

10.2.20 Health Care Provider Consultations not Foreseen by the Protocol

From Entry Visit onwards, health care provider consultations not foreseen by the protocol will be assessed in the CRF. It includes the type of provider [General practitioner (GP), specialist physicians, nurses...], the site of care (office-private, office-hospital, home, emergency room) and the reason. 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. Health care provider consultations not foreseen by the protocol will not be assessed for N01315 subjects.

10.2.21 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, transfers 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. Hospital stay will not be assessed for N01315 subjects.

10.2.22 Non-Antiepileptic and Antiepileptic Concomitant Medications/Non-Antimyoclonic and Antimyoclonic Concomitant Medications

At Entry Visit, the Investigator will record all the non-antiepileptic/non-antimyoclonic and antiepileptic/antimyoclonic 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/ non-antimyoclonic concomitant medications must be recorded on the Non-Antiepileptic/ Non-Antimyoclonic Concomitant Medications page of the CRF. In case of intake of forbidden concomitant medication (Section 9.2.2) during the study period, the Investigator will contact the monitor immediately.

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

Antimyoclonic and non-antimyoclonic medication will only be recorded for ULD subjects.

10.2.23 EQ-5D Questionnaire

The EQ-5D[25] 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 not be completed by subjects with ULD and by subjects coming from N01114 or N01315. 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.

10.2.24 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 and N01254 only. It collects information such as education level, housing status, employment status, need for caregiver and driving license.

10.2.25 End of Study

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 dose. Dose decreases can be made by steps of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for one 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 study drug-free period and subsequently the Final Visit will occur.

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 final status (study completion or reason for early study termination) will be recorded. It will be specified:

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

A subject will be considered lost to follow-up following two documented unsuccessful attempts to contact the subject by telephone.

10.3 Study Conduct

Conduct of the visits is described in Flow chart (Section 4.1). Detailed description of assessments done during different type of visits is described in this section and in Procedures (Section 10.2).

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 Clinical study physician or representative should be contacted for agreement. The Adverse Events, medical procedures, non-antiepileptic/non-antimyoclonic and antiepileptic/antimyoclonic concomitant medication belonging to the interim period will be reported in the CRF, on specific pages.

Each visit will be planned within a "window" of ±7 days from the previous visit. When possible, out-of-window visits should be rescheduled with respect to the Entry 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 adverse events, etc., should be collected in the source documents and recorded in the appropriate section of the CRF.

For subjects coming from therapeutic exploratory studies during the early stage of development, visits will be organized on a monthly basis during the first 6 months, afterwards subjects' visits will be scheduled once every three months.
Coming from confirmatory studies at a later stage of the drug development, subjects will have monthly clinic visits during the first 3 months, afterwards subjects' visits will be scheduled on a-three-monthly basis (Section 4.2). Subjects coming from N01315 will be scheduled on a three-monthly basis.

Note: Procedures performed within the first 2 years are not applicable to subjects coming from N01315.

10.3.1 Entry Visit

- Signing and dating of written informed consent.
- Dispensation of "clinical trial subject card" (participation in the study).
- Verification inclusion/exclusion criteria.
- Demography data: date of birth, gender and racial group.
- Childbearing potential.
- Body weight and height.
- Dispensation of "daily record card".

- Recording of Adverse Events.
- Medical procedures.
- Concomitant medications (AED and nonAED) documentation.
- Concomitant medications (AMD and nonAMD) documentation (for ULD subjects).
- Dispensation of study medication: subject will receive study medication at Entry Visit once all inclusion/exclusion criteria have been met.
- Appointment for the next visit according to schedule described in Section 4.2.

The following data will be transferred electronically from the first visit of the previous study and should not be recorded in the CRF:

- General medical and procedures history.
- Epilepsy history.
- Disease history (for ULD subjects).
- AED history.
- AMD history (for ULD subjects).

The following data will be transferred electronically from the last Evaluation Visit of the previous study and should not be recorded in the CRF:

- Vital signs including blood pressure, pulse rate.
- Physical and neurological examinations.
- ECG.
- Recording of epileptic seizures.
- Laboratory assessment includes safety: blood chemistry, hematology and urinalysis. Urine pregnancy test (β-hCG levels) for women with childbearing potential.

10.3.2 Full Evaluation Visit

- Vital signs including blood pressure, pulse rate.
- Body weight.
- Physical and neurological examinations.
- Retrieval of previous and dispensation of new daily record card.
- Recording of epileptic seizures.
- Laboratory assessment includes safety: blood chemistry, hematology and urinalysis. Urine pregnancy test (β-hCG levels) for women with childbearing potential.
- Recording of Adverse Events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and nonAED) documentation.
- Concomitant medications (AMD and nonAMD) documentation (for ULD subjects only).
- Drug return/accountability include study medication intake and compliance check.
- Dispensation of study medication.

- Appointment for the next visit according to schedule described in Section 4.2.

The following assessments will be performed during the first 2 years which includes the YEV in year 3

- QOLIE-31-P assessment: the questionnaire should be filled in at the beginning of the Visit (not for ULD subjects).
- HADS: the questionnaire should be filled in at the beginning of the Visit, after the QOLIE-31-P (not for ULD subjects).
- Health care 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 for subjects coming from N01252 and N01254.

10.3.3 Minimal Evaluation Visit

- Vital signs including blood pressure, pulse rate.
- Retrieval of previous and dispensation of new daily record card.
- Recording of epileptic seizures.
- QOLIE-31-P assessment: the questionnaire should be filled in at the beginning of the Visit at the MEV in Month 3 (for ULD subjects and subjects coming from N01114).
- Recording of Adverse Events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Health care provider consultation not foreseen by protocol during the first 2 years.
- 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.
- Concomitant medications (AED and nonAED) documentation.
- Concomitant medications (AMD and nonAMD) documentation (for ULD subjects only).
- Drug return/accountability include study medication intake and compliance check.
- Dispensation of study medication.
- Appointment for the next visit according to schedule described in Section 4.2.

10.3.4 Yearly Evaluation Visit (replaces the FEV of each year)

- Vital signs including blood pressure, pulse rate.
- Body weight.
- Height for subject still in growing period.
- Physical and neurological examination.
- ECG.

- Retrieval of previous and dispensation of new daily record card.
- Recording of epileptic seizures.
- Laboratory assessment includes safety: blood chemistry, hematology and urinalysis. Urine pregnancy test (β-hCG levels) for women with childbearing potential.
- Recording of Adverse Events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and nonAED) documentation.
- Concomitant medications (AMD and nonAMD) documentation (for ULD subjects only).
- Drug return/accountability include study medication intake and compliance check.
- Dispensation of study medication.
- Appointment for the next visit according to schedule described in Section 4.2.

The following assessments will be performed during the first 2 years which includes the YEV in year 3

- QOLIE-31-P assessment. The questionnaire should be filled in at the beginning of the Visit.
- HADS: the scale should be filled in at the beginning of the Visit (except for ULD subjects).
- Health care 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 for subjects coming from N01252 and N01254.
- Socio-professional data for subjects coming from N01252 and N01254.

10.3.5 Early Discontinuation Visit

- Vital signs including blood pressure, pulse rate.
- Body weight.
- Physical and neurological examination.
- ECG.
- Retrieval of previous and dispensation of new daily record card.
- Recording of epileptic seizures.
- Laboratory assessment includes safety: blood chemistry, hematology and urinalysis. Urine pregnancy test (β-hCG levels) for women with childbearing potential.
- Recording of Adverse Events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Concomitant medications (AED and nonAED) documentation.
- Concomitant medications (AMD and nonAMD) documentation (for ULD subjects only).

- Drug return/accountability include study medication intake and compliance check.
- Dispensation of study medication with down-titration dosing schedule.
- Appointment for the next visit according to schedule described in Section 4.2.
- Down-titration.

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

- QOLIE-31-P assessment: the questionnaire should be filled in at the beginning of the Visit.
- HADS: the scale should be filled in at the beginning of the Visit (except for ULD subjects).
- Health care 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 for subjects coming from N01252 and N01254.
- Socio-professional data for subjects coming from N01252 and N01254.

10.3.6 Down-Titration Phone Call

- Recording of Adverse Events.
- Remind appointment for the next visit according to schedule described in Section 4.2.

10.3.7 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, pulse rate.
- Body weight.
- Height for subject still in growing period.
- Physical examination.
- Neurological examination.
- ECG (except after an EDV when EDV ECG results were normal).
- Retrieval of previous daily record card.
- Recording of epileptic seizures.
- Laboratory assessment has to be scheduled (except after an EDV when EDV laboratory results were normal). Laboratory assessment includes safety: blood chemistry, hematology and urinalysis. Urine pregnancy test (β-hCG levels) for women with childbearing potential.
- Recording of Adverse Events.
- Assessment of suicidality (C-SSRS).
- Medical procedures.
- Health care provider consultation not foreseen by protocol during the first 2 years.

- 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.
- Concomitant medications (AED and nonAED) documentation.
- Concomitant medications (AMD and nonAMD) documentation (for ULD subjects only).
- Drug return/accountability including study medication intake and compliance check.
- End of study status
- Return of "Clinical Trial Patient Card".

10.3.8 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, medical procedures, concomitant AEDs and nonAEDs, concomitant AMDs and nonAMDs (for ULD subjects only), should be collected in the source documents and recorded in the appropriate section of the CRF. Study medication can be dispensed if required.

If an Additional Visit is conducted for safety or efficacy reasons, a C-SSRS assessment will be performed during this visit. If an Additional Visit is conducted for reasons other than safety or efficacy issues (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at this visit.

10.4 Handling of Biological Samples

The safety samples (hematology, biochemistry, urinalysis, pregnancy test) will be routinely assayed and the results sent by fax to the Investigators as specified in Section 10.2.16.

Urine samples must be collected under hygienic conditions and transferred by study site staff in vacutainer tubes.

10.5 Other Supplies

At Entry Visit (or First Visit for subjects coming from N01315), each subject will receive a study card that will mention his/her participation in the study, indicating the name and phone number of the Investigator to be contacted in case of emergency and the name of the study product concerned. Participation in the study will be mentioned in the subject's clinical records.

11. ASSESSMENT OF EFFICACY

11.1 Specifications of Efficacy Variables

The procedures for obtaining the data of the efficacy variables are found in Section 10.2. The complete list of variables to be analyzed is found in Section 13.1.2.1.

11.2 Methods and Timing for Assessing, Recording, and Analyzing the Efficacy Variables

The methods and timing for assessing and recording the efficacy variables are found in Section 4.2 and in Section 10.3.

The analysis methods are found in Section 13.1.3.

12. ASSESSMENT OF SAFETY

12.1 Specifications of Safety Variables

Safety assessments will be made using adverse events, laboratory tests (including blood and urine), electrocardiogram (ECG), physical and neurological examinations, vital signs, and body weight.

The procedures for obtaining the data of the safety variables are found in Section 10.2. The complete list of variables to be analyzed is found in Section 13.1.2.1.

12.2 Methods and Timing for Assessing, Recording, and Analyzing the Safety Variables

The methods and timing for assessing and recording the safety variables are found in Section 4.2 and in Section 10.3. The analysis methods are found in Section 13.1.3.

12.3 Adverse Events

12.3.1 Definition of Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and 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. In the event subjects terminate study participation after signing informed consent but prior to any study procedures being conducted, adverse events will not be recorded on the CRFs.

Signs or symptoms of epilepsy 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.

12.3.2 Procedures for Reporting and Recording Adverse Events

12.3.2.1 Recording/Collection of AEs

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.

12.3.2.2 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. 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 of 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 charge	Investigational product dosing remained the same in spite of AE being present.
Dosage changed	Investigational product dose was increased or 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:	
None	No other action was taken for this AE.
Concomitant medication	Drug treatment: the subject took a concomitant medication (either prescription or non-prescription) specifically for this AE OR existing concomitant medication dosage was modified as a result of this AE.

Hospitalization or prolongation of hospitalization	The subject was hospitalized for this AE or subject's stay in hospital was prolonged because of this AE.
Therapeutic or diagnostic procedure	Subject used other therapeutic measures (e.g. ice, heating pad, brace, cast, etc.) or subject underwent a diagnostic procedure (e.g., additional lab test, x-ray, etc.) for this AE.
Date of outcome:	Date (and time) the AE abated. If the AE consists of several signs and symptoms (syndrome), 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.
Resolved	The AE is no longer present at any intensity - completely abated.
Resolved with sequelae	The AE is resolved but residual effects are still present.
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 subject's death.
Ongoing	The AE is still present at the last contact with the subject.
Relationship to investigational product:	
None	only applicable when no investigational product was taken or when the subject is taking single-blind placebo, or when the AE can be ascribed with reasonable certainty to another cause.
Unlikely	there are good reasons to think that there is no relationship, e.g. the AE is a known adverse drug reaction of a concomitant medication.
Possible	equally valid arguments can be considered for or against an implication of the investigational product, e.g. 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, e.g. 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
Highly probable	there is a strong relationship, e.g. the AE: • follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissues; • follows a known or expected response pattern to the investigational product; • is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the AE on repeated exposure (rechallenge).

12.3.3 Follow-up of Adverse Events

If an AE is still ongoing at the time the last CRF is being collected, a follow-up report should be provided at a later date.

If no follow-up report is being 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. rechallenge procedure).

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

12.3.4 Rule for Repetition of an AE

An increase in the intensity of an AE should lead to the repetition of the AE reporting with:
- the outcome date of the first AE 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, so that they code to the same dictionary term.

12.3.5 Pregnancy

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

The progression of the pregnancy and eventual birth must be followed up using the Sponsor's standard Pregnancy & Delivery form in which the Investigator reports 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.

12.3.6 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 "Trial Medication Intake" section of the CRF.

12.4 Serious Adverse Events

12.4.1 Definition of Serious Adverse Event (SAE)

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

- Results in death.
- Is life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity, or.
- Is a congenital anomaly/birth defect.

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

Any important medical event that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one 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 procedure 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.

12.4.2 Procedures for Reporting Serious Adverse Events (SAE)

If a SAE is reported, the Sponsor or its representative must be informed within 24 hours of receipt of this information by the site (see emergency contact information on front page). The Investigator must promptly forward to the Sponsor or its representative a duly filled in "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 in order to draw any conclusions.

The SAE report form and the completion guide will be provided by the monitor to the Investigator. The SAE report form has to be completed in English.

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 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 (Suspected Unexpected Serious Adverse Reaction – SUSARs) to the appropriate Regulatory Authorities and all active Investigators, in accordance with applicable regulatory requirements. The appropriate IEC/IRB will also be informed by the Investigator or by 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 the completion guide will be provided by the monitor.

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.

12.4.3 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.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.4.2.

13. STATISTICS

A general description of statistical methods is presented below. Additional detail will be described in the Statistical Analysis Plan (SAP). Statistical analyses of data for subjects transferring from N01315 will be handled as described in the SAP.

13.1 Statistical and Analytical Plans

13.1.1 Study Population(s)

- Subpopulations

There are 3 mutually exclusive subpopulations. They are defined based upon enrollment.

1. Partial onset seizure: Subjects enrolled from prior studies N01114, N01252, 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

3. Unverricht-Lundborg disease: Subjects enrolled from prior studies N01187 and N01236

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 Study variables

13.1.2.1 Safety Variables

- Primary safety variables
  - Occurrence of a TEAE
  - Withdrawal due to AE
  - Occurrence of an SAE

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

13.1.2.2 Efficacy Variables

- Secondary efficacy variables

  For subjects with focal-onset epilepsy:
  - Partial onset seizure (type I) frequency per 28 days during the Evaluation Period.
  - Percent reduction in POS (type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period.
  - 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.

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

- 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 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.
  - 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.

13.1.2.3 Pharmacoeconomic Variables

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

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

No pharmacoeconomic variables are defined for subjects with ULD.

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 and separately for the POS, PGS, and ULD subpopulations within 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 change 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. The ULD subpopulation seizure diary data will not be summarized.

- QOLIE-31-P and EQ-5D 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. The ULD subpopulation QOLIE-31-P and EQ-5D data will not be summarized.

- Pharmacoeconomic 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. The ULD subpopulation pharmacoeconomic data will not 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 adverse events will be summarized by categories of total duration of exposure, period, and Medical Dictionary for Regulatory Activities (MedDRA®) Primary System Organ Class and Preferred Term in incidence tables. Separate tables will be provided, by categories of total duration of exposure, for AEs leading to withdrawal from the study and SAEs.

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/PGS subpopulation only.

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 or Missing Data

Safety and efficacy variables will be analyzed as they are available. Days with missing information will be ignored in the calculation of the seizure frequency 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 two 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 and medical and surgical history will be coded according to the MedDRA dictionary. Coding of indications of concomitant medication has been stopped during the course of the study.

Medications will be coded according to the World Health Organization (WHO) Drug dictionary.

14. ETHICS

14.1 Approval

When finalized, the protocol must be signed by the Principal Investigator of the site, the Sponsor Clinical Study Physician, the Sponsor Clinical Program Director, the Sponsor Statistician, and the Sponsor Clinical Trial Manager (CTM). The final version must be submitted to and approved by:

- a duly constituted IEC/IRB.
- the relevant 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 Clinical Study Physician, the Clinical Program Director, the Statistician, the CTM, and the Sponsor approval committee(s) and this before further submission to the requesting body.

A copy of the written IEC/IRB 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. In addition, for the sites under IND: The usual composition of the IEC/IRB (or DHHS number) along with an IEC/IRB statement of compliance should also be forwarded to the CTM.

The study is not allowed to start until the protocol and related documents (Subject Information Sheet/Informed Consent, advertisements if any, …) have received written approval/favorable opinion from the IEC and Regulatory Authorities, wherever required as well as until other GCP prerequisites are fulfilled.

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

14.2 Subject Information and Consent

Adequate information will be provided to the subject and parent(s) or legal representative, if applicable, in both oral and written form and consent will be obtained in writing prior to the performance of any study specific procedure. The content and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

The Sponsor may provide a sample Informed Consent Form/subject information sheet. The final form must be agreed by the IEC/IRB and must contain all ICH-GCP (4.8.10) elements in a language readily understood by the subject.

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.

14.2.1 Information

The Investigator, or a person designated by the Investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the parent(s) or legal representative, of all pertinent aspects of the study, including the fact that the protocol has been granted, the approval of the IEC/IRB and local regulatory authorities if required.

The subject will be informed of the nature of the study in an unambiguous, easily understandable language. The subject's participation is voluntary. The subject can at any time withdraw consent without any influence on future care or treatment. The subject must be informed about the main procedures used to guarantee anonymity, especially during the analysis of personal data. The subject should be able to ask all the questions about the study and to receive relevant answers. The subject will receive complete written information in the "Subject Information Sheet".

14.2.2 Informed Consent

After having received extensive information about the nature, significance, implementation and risks of the study and having had enough time to consider, the subject must give his/her written consent by signing and dating the Informed Consent Form. For minors, the informed consent must be signed by the parent(s) or legal representative, in accordance with local regulations. The consent form or a specific assent form, where required, will be signed and dated by minors. For mentally retarded subjects, the Informed Consent Form must be signed by the legal representative.

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.

This form will also be dated and signed 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 chart and in the CRF.

Two copies of the Informed Consent Form will be signed. The subject will receive one and the other will be filed in the Investigator's Site File.

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

If any relevant new information that could influence the subject's decision to stay in the study becomes available, this will be transmitted without delay to the subject and the Investigator.

The Investigator will keep up to date a Subject Identification List, i.e. a log of all subjects having entered the study by signing an Informed Consent Form. This log is to be filed in the Investigator Site File.

14.3 Subject Confidentiality

Subject confidentiality will be maintained at all times.

Personnel from the Sponsor, from the CRO, from Regulatory Authorities, independent auditors and members of IEC/IRB are obliged to respect medical secrecy and to refrain from divulging the subject's identity or any other personal information they might fortuitously be aware of. Medical records will be handled by professional standards and existing local laws.

14.4 Informing the General Practitioner

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

15. STUDY MANAGEMENT AND ADMINISTRATION

15.1 Monitoring

The monitoring of the study is the responsibility of the Sponsor. The monitor (the individual responsible for monitoring) will help the Investigator with the practical conduct of the study and assist him/her in working according to the protocol, Good Clinical Practice (GCP), and the regulatory requirements.

The Investigator will allow the Sponsor or its representatives to periodically monitor at mutually convenient times during and after the study, all CRFs and the corresponding portions of source documents (e.g. 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, to ensure that all protocol

requirements, applicable local Authority regulations and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

15.2 Direct Access to Source Data/Documents

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

Source documents (SD) are original records in which raw data are first recorded. These may be: hospital/clinic/general practitioner (GP) records, charts, diaries, x-rays, laboratory results, printouts, ECG tracing and reports and EEG tracing and reports, pharmacy records, care records, etc.

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 a permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correcting fluid or have temporary attachments (such as "post-it" notes).

Source documents that are computer generated and stored on magnetic support media must be printed. The Investigator will sign and date the print-out and the monitor will counter-sign these print outs after monitoring. The Investigator will authorize the monitor to compare the content of the print-out and the data stored in the computer to ensure all data are consistent.

The minimum requirements for source data in the medical records used in clinical studies are that they should contain: the identity of the subject and a study related identifiers (such as treatment number, CRF number or similar), a note of the subject's participation in the study and identification of that study (protocol/study title or number), the date of obtaining signed informed consent, the subject's medical history, the treatments that the subject received, AEs and SAEs and the dates of the visits. The source documents should also provide evidence that inclusion/exclusion criteria were evaluated and met. Information recorded in the CRF must be consistent with entries in the source document. The monitor will verify 100% of the source documents against the CRFs.

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 main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, and that all data relevant for the evaluation of the

investigational product have been processed and reported in compliance with the planned arrangements, GCP and applicable regulatory requirements. The Investigator will provide direct access to all study documents, source records and source data. If an inspection by Health Authorities is announced, the Investigator will immediately inform the Sponsor.

15.4 Case Report Forms (CRF)

Data reflecting participant experience with the drugs 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.

The CRF will be organized in Yearly Books and general section workbooks. CRFs will be signed and dated by the Principal Investigator as indicated.

The CRF will be adapted to reflect the changes in the study assessments. It will be used after the approval of the Ethics Committee and after the subjects have signed the new Informed Consent Form.

The Principal Investigator's signature on the CRF attests to its accuracy and completeness. The CRFs will be completed in black ink, and must be legible.

Data reported in the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained in these 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 or hospitalization records, must be clearly identified with the study number, study participant number, and study participant initials; any personal information, including the study participant's name, must be removed or rendered illegible to preserve individual confidentiality.

15.5 Adherence to Protocol

The Investigator/Institution should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the Regulatory Authority(ies) and for which an approval/favorable opinion by the IEC/IRB was given. 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 in or deviations from the protocol will ONLY be made as an amendment to the protocol and must be approved by the Sponsor and the IEC/IRB prior to being implemented. Unless the Sponsor has consented to any such deviations or changes in writing, they cannot be implemented and the Sponsor will not assume any resulting responsibility or liability for implementation of unapproved deviations or change.

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 Study Report.

15.6 Termination of the Study

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

- Return of all study data to the Sponsor or its representative.
- 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.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues, severe non-compliance, recurrent non-compliance, with respect to quality or quantity.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions, and the regulatory authority(s) of the termination or suspension and the reason(s) for the termination or suspension. The IEC/IRB should also be informed promptly and provided with the 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 all unused study drugs in accordance with the Sponsor procedures for the study.

15.7 Investigator Site File

The content of the Investigator file is structured in a manner that aids in the filing, retrieval, and/or auditing of study-related documents. All documents will be filed according to Standard File Categories that identify specific aspects of the study.

15.8 Data Handling and Record Keeping

The Sponsor will be responsible for data processing.

CRF data will be entered in an 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 interactive double data entry. The SAS system will be used for the statistical analysis of the data. Regular back-ups of the electronic data will be carried out.

15.9 Clinical Study Report

A clinical study report, conforming to the relevant ICH guidelines, will be prepared by the Sponsor. The report will include a thorough description of the clinical and laboratory methods, a discussion of the results and a list of all measurements.
This report may be included in submissions to government Drug Regulatory Authorities world-wide, or used for whatever reason considered appropriate by the Sponsor. No use should be made of the report before approval by the Sponsor.

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

15.10 Subject Insurance

The Sponsor declares that it has taken out an insurance, for the total duration of the study, covering the subjects (and for US sites only: Investigators, employees or co-workers of Investigators assisting with the study), in respect of the risks involved in this study according to this protocol. In case of injury or disability deriving from participation in the study, the subject is requested to inform without delay the treating physician responsible for the study.

15.11 Archiving and Data Retention

The Investigator will maintain adequate records for the study including CRFs, medical records, laboratory reports, informed consent documents, drug 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 Trial 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. He/she remains responsible for coordinating and informing his/her staff about the protocol and the possible changes made to it.

The Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties ("authorized signatures" document with name, function, signature, initials, dates of participation in the study and type of delegated tasks). This list should be kept up to date.

15.13 Curriculum Vitae

The Investigators should supply their updated curriculum vitae (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.

In addition, for ULD sites under IND, a signed and dated FDA Form 1572 (Qualified Investigator Undertaking and Clinical Trial Site Information forms in Canada) and recent (updated every 2 years) CV (in English) are required from each Investigator showing a current affiliation with the research center.

15.14 Financial Disclosure

A financial disclosure statement must be obtained from each clinical site for every Investigator and co-Investigator participating in the study. This must be collected before subject enrollment. They 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.

16. REFERENCES

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12. A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 used as adjunctive treatment at doses of 50 and 150 mg/day in b.i.d. administration (oral capsules of 25 mg) for a maximum of 12 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized. UCB study number N01114. UCB protocol reference code RPCE02K0301.
13. A multicenter, double-blind, randomized, placebo-controlled, 4 parallel groups, dose-ranging trial evaluating the efficacy and safety of brivaracetam used as adjunctive treatment at doses of 5, 20 and 50 mg/day in b.i.d. administration (oral tablets of 2.5 or 10 mg) for a maximum of 7 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized. UCB study number N01193. UCB protocol reference code RPCE05C2201.

14. A multi-center, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with Partial Onset Seizures. UCB study number N01252. UCB protocol reference code RPCE06G0704.
15. An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with Partial Onset Seizures UCB study number N01253. UCB protocol reference code RPCE06G0705.
16. A multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of brivaracetam used as adjunctive treatment for 12 weeks in adolescent and adult patients (≥16 years) with genetically ascertained Unverricht-Lundborg disease. UCB study number N01187. UCB protocol reference code RPCE06C2321.
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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 current Good Clinical Practice.

N01125 Protocol Amendment 27 Integrated

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	17-Mar-2015 21:30 GMT+01
	Clinical Approval	17-Mar-2015 23:33 GMT+01