PROTOCOL EP0073 AMENDMENT 3

AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF UCB0942 WHEN USED AS ADJUNCTIVE THERAPY FOR PARTIAL-ONSET SEIZURES IN ADULT SUBJECTS WITH HIGHLY DRUG-RESISTANT FOCAL EPILEPSY

PHASE 2

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LIST OF ABBREVIATIONS

50%RR	50% responder rate
75%RR	75% responder rate
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
BRV	brivaracetam
cBZR	benzodiazepine-binding site
CDMS	clinical data management system
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
CMR	cardiac magnetic resonance
CNS	central nervous system
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DDI	drug-drug interaction(s)
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EDV	Early Discontinuation Visit
EMA/EMEA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EV	Entry Visit
FAS	Full Analysis Set
FEV	Full Evaluation Visit

FV	Final Visit
GABA-A	gamma-aminobutyric acid receptor type A
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRT	interactive response technology
LEPV	Last Evaluation Period Visit
LEV	levetiracetam
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
MEV	Minimal Evaluation Visit
MMSE	Mini-Mental State Examination
OLE	open-label extension
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
POS	partial-onset seizure
PS	Patient Safety
QOLIE-31-P	Quality of Life Inventory in Epilepsy-31-P
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SFU	Safety Follow-Up
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SV2	synaptic vesicle glycoprotein 2
TC	Telephone Call
TEAE	treatment-emergent adverse event

ULN	upper limit of normal
V	Visit
VNS	vagus nerve stimulation
Wk	Week
YEV	Yearly Evaluation Visit

1 SUMMARY

UCB0942 is a new chemical entity with selective affinity for synaptic vesicle glycoprotein 2 (SV2) and for the benzodiazepine-binding site (cBZR) on the gamma-aminobutyric acid receptor type A (GABA-A). UCB0942 has shown superior efficacy in several preclinical models of epilepsy.

EP0073 is an open-label extension (OLE) study that will run throughout the clinical development period of UCB0942 and will continue for approximately 5 years or until either a marketing authorization is granted by any health authority for the adjunctive treatment for partial-onset seizures (POS) in adult subjects with highly drug-resistant focal epilepsy, or until UCB decides to close the study.

Subjects who experience substantial benefit from UCB0942 with acceptable tolerability in EP0069 may have the opportunity to continue UCB0942 treatment in this OLE study. The decision to enter this study must be made by the Investigator in consultation with the subject and his/her caregiver. The Investigator's decision must take into account the benefit experienced and the potential risks of long-term exposure to UCB0942, as well as the potential benefit and risks of other treatment options available.

A Data Monitoring Committee (DMC) will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the investigational medicinal product (IMP). The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, or termination of the clinical study.

The study will consist of:

- A 2-week Screening Period from Visit 13 (V13) to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study. At this visit, informed consent will be signed and inclusion and exclusion criteria (from the current OLE study) will be checked. The verbatim of the attained benefits of treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be captured as narratives and filled in by the Investigator or site personnel. During the Screening Period, the Investigator will also provide a statement and a brief justification of the benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942. These narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be maintained as source documents and will be reviewed by the DMC.
- An Evaluation Period of up to approximately 5 years, which will start with V2, the Entry Visit (EV), which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Eligible subjects will enter EP0073 before the planned dose tapering in EP0069. Subjects will be issued and return seizure diaries during each visit. Subjects must be

educated to record all types of seizures that occur, any illness or injury, and all study medication intake in their seizure diary and be educated to complete their diary entries after each seizure or at least once a day. Throughout the study, the Investigator also will be requested to periodically re-assess and re-confirm that the benefit-risk ratio for the subject on long-term treatment with the IMP, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options, justifies continuation in the study. Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at the scheduled time points presented in Table 5–2.

First year:

In the first month of EP0073, subjects will have Telephone Calls (TCs) (Month [M]1-Week [Wk]1 [TC1] and M1-Wk3 [TC2]) and 1 clinic visit (M1-Wk2 [V3]). During the 2 TCs, the site personnel will review changes in concomitant medications (including antiepileptic drugs [AEDs]), confirm whether the subject experienced any adverse events (AEs)/serious adverse events (SAEs), and ensure that subjects are compliant with their study medication dosing schedule as outlined in the protocol.

During the second, third and fourth months, subjects will visit the clinic at M2 (V4, Minimal Evaluation Visit [MEV]), M3 (V5, Full Evaluation Visit [FEV]), and M4 (V6, MEV).

Subjects will return to the clinic every 3 months for the remainder of the first year with FEV alternating with MEV: M7 (V7, FEV) and M10 (V8, MEV).

Second and third year:

For the second and third years, subjects will have clinic visits every 3 months, with MEVs alternating with FEVs/Yearly Evaluation Visits (YEVs), beginning with M13 (V9, YEV).

Fourth and fifth year:

- For subjects who continue to participate in EP0073 beyond the 3-year period, the subjects will have a clinic visit every 6 months with YEVs alternating FEVs.
- A Taper Period starting at the Last Evaluation Period Visit (LEPV) of the Evaluation Period; during the Taper Period, subjects will start to gradually decrease their dose of UCB0942. The Taper Period is planned to be 3 weeks, however a faster taper schedule than the suggested 3 weeks may be implemented if medically necessary. A slower taper schedule of up to 6 weeks may be implemented as per the Investigator's medical judgment.
- A Safety Follow-Up (SFU) Period; subjects must return to the clinic 1 week after administration of the final dose of UCB0942 (SFU1). A Final Visit (FV) will be scheduled 30 days after administration of the final dose of UCB0942 (SFU2).

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster

decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg twice daily [bid]), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. Exceptions may be allowed after consultation with the PRA Medical Monitor. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AEDs and AED dose(s), or vagus nerve stimulation (VNS) settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction.

If at any time the subject and/or the Investigator decide to discontinue UCB0942, the subject should return for an Early Discontinuation Visit (EDV) and gradually decrease their dose of UCB0942.

For each subject, the study will last from study entry for approximately 5 years or until either regulatory approval of UCB0942 has been granted by any health authority for the adjunctive treatment for POS in adult subjects with highly drug-resistant focal epilepsy, or until UCB decides to close the study.

The primary objective of this study is to evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 100mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy. The secondary objectives are to evaluate the long-term efficacy of UCB0942 and to evaluate the effects of UCB0942 on the subject's quality of life using the Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P; Cramer et al, 2003). The exploratory objective is to evaluate the plasma concentrations of UCB0942 and metabolites.

The primary safety variable is the occurrence of AEs reported by the subject and/or caregiver or observed by the Investigator or clinical site staff beginning at the EV of the Evaluation Period during the EP0073 study.

Other safety variables are:

- Changes from EP0069 baseline in laboratory tests (including hematology, blood chemistry, urinalysis) at each assessment during the EP0073 study
- Changes from EP0069 baseline in 12-lead electrocardiogram (ECG) parameters at each assessment during the EP0073 study
- Changes from EP0069 baseline in psychiatric assessments as assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) at each assessment during the EP0073 study
- Changes from EP0069 baseline in memory or cognition as assessed with the Mini-Mental State Examination (MMSE; Folstein et al, 1975) at each assessment during the EP0073 study

- Changes in withdrawal symptoms using the Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B; Busto et al, 1989) from the LEPV (last visit prior to Taper Period), at each assessment during the Taper Period (visit at the end of the Taper Period) and during the SFU Period (visits at 1 week and 30 days after administration of the final dose of UCB0942) of the EP0073 study
- Changes from EP0069 baseline in vital sign parameters (pulse rate, blood pressure [BP], and respiratory rate [RR]) at each assessment during the EP0073 study
- Occurrence of a clinically concerning valvular or pericardial effusion change or other clinically significant abnormalities as identified by 2-dimensional Doppler echocardiography at each assessment during the EP0073 study
- Changes from EP0069 baseline in physical examination (including body weight) and neurological examination findings at each assessment during the EP0073 study.

With regard to efficacy, in both this study and EP0069 only POS of type IA1, IB, and IC and not non-motor IA2, IA3 or IA4 seizures will be counted for the assessment of seizure frequency and responder rate. For assessment of seizure-free rate and days, all seizure types will be considered.

The primary efficacy variable is the 75% responder rate (75%RR) by 3-month intervals over the Evaluation Period. A 75% responder is defined as a subject with a ≥75% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069.

Secondary efficacy variables are described in Section 4.2.2 and the exploratory pharmacokinetic (PK) variable is described in Section 4.3.

2 INTRODUCTION

2.1 General background

In Europe and North America, there are approximately 350 to 500 thousand (3 to 4 million worldwide) patients with focal epilepsy who have not been able to achieve freedom from disabling seizures despite sequential and/or combination treatment with several of the available AEDs. Even with the introduction of 12 new AEDs over the last 2 decades, the proportion of patients with epilepsy who are unable to achieve complete control of their seizures has only decreased minimally, from 36% to 34% (Brodie et al, 2012), highlighting this large unmet medical need and the fact that recently developed AEDs have not been able to meet this medical need.

The likelihood of achieving complete seizure control diminishes further as the number of failed AEDs regimens increases. Thus, when a patient with focal epilepsy has not been able to control their seizures despite treatment with 4 or more AED regimens, the likelihood of achieving complete seizure control with another AED regimen is 1% to 4% (Schiller and Najjar, 2008; Mohanraj and Brodie, 2006; UCB internal data on lacosamide and brivaracetam [BRV]). This group of patients, who are the target population for this study, will be referred to as having "highly drug-resistant focal epilepsy."

Although resective surgery is an option for some patients with drug-resistant focal epilepsy, fewer than 1% of patients with drug-resistant focal epilepsy are evaluated for epilepsy surgery due to various factors (limited number of epilepsy surgery centers, lack of referral, inability to localize the seizure focus during work-up, contraindications to surgery, etc.; Engel, 2013).

Therefore, the vast majority of patients with highly drug-resistant focal epilepsy have no treatment options (pharmacological or surgical) that can provide complete seizure control or even substantial reduction in the number of seizures.

In patients with uncontrolled focal epilepsy, seizures increase the risk of mortality and have a negative impact on psychosocial functioning and quality of life across multiple dimensions. Patients with drug-resistant focal epilepsy and complex-partial or tonic-clonic seizures have 5 to 10 times higher mortality rate (Fazel et al, 2013; Hesdorffer and Tomson, 2013; Holst et al, 2013; Sperling, 2004) including risk of sudden unexplained death in epilepsy (Devinsky, 2011). Moreover, drug-resistant focal epilepsy is regarded by many experts as a progressive disease in which ongoing seizures result in an increased risk of further seizures. These patients are prone to falls and injuries; they cannot drive and can rarely live independently; they feel isolated and stigmatized; they have difficulty finding and keeping a job and often depend on disability benefits (Azuma and Akechi, 2014; Taylor et al, 2001; Baker et al, 1997). A treatment that provides seizure freedom will reduce mortality (Laxer et al, 2014) and significantly improve quality of life (Choi et al, 2014; Baker et al, 1997) by increasing their ability to attain basic safety, freedom from the risk of falls and injuries, and reach the milestones that most people take for granted: a feeling of belonging and social integration, the ability to form intimate relationships and a family, and having a productive and rewarding profession or other means of self-realization.

UCB0942 has shown superior efficacy in several preclinical models of epilepsy. UCB0942 is superior to levetiracetam (LEV) and BRV in 10 animal models of focal and generalized epilepsy, indicating that it has broad antiseizure effects. In the rat amygdala kindling model – a model of drug-resistant focal epilepsy – UCB0942 is superior to 12 other AEDs tested thus far: LEV, BRV, phenytoin, phenobarbital, carbamazepine, lacosamide, valproate, retigabine, perampanel, clobazam, diazepam, clonazepam, and the combination of LEV or BRV with diazepam. In this model of drug-resistant focal epilepsy, UCB0942 was the only compound that produced complete seizure suppression in all animals at a plasma exposure equivalent to the plasma exposure achieved in humans taking UCB0942 400mg bid. Other AEDs produced seizure suppression in this model, but only at plasma exposures that are unattainable in humans.

Based on its superior preclinical efficacy profile, UCB0942 may show efficacy in patients with focal epilepsy who continue to suffer from frequent seizures despite having attempted to achieve seizure control with multiple AED regimens (patients with highly drug-resistant focal epilepsy). If seizure freedom or a substantial reduction in seizure frequency could be achieved in these patients, their quality of life would dramatically improve, and this improvement is expected to outweigh the potential risks associated with the administration of UCB0942.

Preclinical experience with UCB0942 is described extensively in the Investigator's Brochure.

2.2 Clinical experience

UCB0942 has completed Phase 1 development with a total of 145 subjects exposed to single doses up to UCB0942 490mg and multiple doses up to UCB0942 400mg bid for up to 14 days, including 20 subjects with epilepsy at 400mg bid. There were no clinically significant changes in laboratory tests or vital signs thought to be related to UCB0942 during Phase 1 development, although transient, minor reductions in systolic and diastolic BP were seen (consistent with the known effects of benzodiazepine drugs). There were no clinically significant changes attributed

to UCB0942 in 12-lead ECGs; however, 4 subjects had treatment-emergent rhythm disturbances (atrial and ventricular ectopy). These were asymptomatic and were assessed by an external expert in cardiology and electrophysiology as unlikely to be related to UCB0942.

The safety findings to date suggest that the AE profile in subjects receiving single and repeated doses of UCB0942 is defined mostly by central nervous system (CNS) effects. At UCB0942 300mg bid and above the AEs tend to be of slightly greater severity and persistence than at doses below 300mg bid. In broad terms, the AEs are consistent with the safety profiles of SV2A and GABA-A targeting AEDs, and common CNS AEs include headache, nausea, somnolence, fatigue, dizziness, balance disorder, disturbance in attention, and memory impairment. Modeling of the relationship between dose or plasma exposure, time, and AEs showed that 1) headache, fatigue, somnolence, balance disorder, and disturbance in attention are dose-dependent AEs; 2) tolerance develops for disturbance in attention and balance disorder; 3) tolerance does not seem to develop for fatigue, somnolence, and headache; and 4) titration will reduce the likelihood that a subject experiences most of these AEs.

2.3 Risks and mitigation strategy

The important identified risks based on clinical data include the development of acute psychiatric effects and drug-drug interactions (DDIs) with strong cytochrome P450 (CYP) 3A4 enzyme inducers leading to decreased exposure levels of UCB0942. There are also some important potential risks that are UCB0942-specific based on clinical data, including impairment of cognitive and psychomotor performance, DDI between UCB0942 with CYP2C19 substrates leading to increased levels of these substrates, and decrease in blood pressure. In addition, there are several potential risks for UCB0942 that are class effects or known for other products, including suicidality, worsening of seizures, substance abuse and dependence, tolerance to the anticonvulsant effects of the drug, and decreased bone mineral density. Finally, there are a number of potential risks that are UCB0942-specific based on nonclinical data, including epicardial and valvular inflammation and epicardial fibroplasia with administration longer than 13 weeks, QT prolongation, hepatoxicity, DDI with strong CYP3A4 inhibitors leading to increased exposure levels of UCB0942, DDI with strong CYP2C19 inhibitors or inducers leading to increased or decreased exposure levels of UCB0942, and growth retardation.

All identified and potential risks, with the exception of decreased growth (applicable only to pediatric studies) will be appropriately mitigated in the proposed clinical study. Clinical data from the completed study EP0069 have been reviewed by a DMC that included internal UCB and external medical experts. Data from this study and any other relevant data that become available (such as preclinical data) will be reviewed by the DMC in order to detect and characterize as early as possible any concern(s) related to UCB0942 (see Section 11.1.8). Investigators, clinical study subjects, regulatory authorities, and Institutional Review Boards/Independent Ethics Committees (IECs) will be informed in a timely manner of any significant information that affects the benefit-risk balance of the UCB0942 and participation in the study. The specific mitigation measures for cardiac AEs, psychiatric events and drug-drug interactions are discussed further below, and additional details about risks and mitigation strategy are provided in Section 6 of the Investigator's Brochure.

2.3.1 Cardiac adverse events

In the 39-week dog toxicology study, subtle cardiac microscopic findings were observed, consisting of minimal inflammatory cell infiltration in the aortic and mitral valves (in 3 out of 24 dogs) and minimal to slight epithelial inflammation (fibroplasia) in the right atrial epicardium (in 5 out of 24 dogs). The epicardial findings were active (ie, there is a potential for progression), while the valvular findings were not active. The histopathology in the 39-week dog study was reviewed by 4 pathologists, including one who is an expert in cardiac pathology, and they concluded that the findings were subtle and not adverse for the dogs. A cardiologist concluded that the potential cardiac hazard of UCB0942 in humans is likely minimal; however, it is possible that epicardial or valvular structural changes will occur in humans with prolonged exposure (beyond 3 months).

Therefore, in this study, subjects will have an echocardiogram at Visit 2 and every 3 months for the first year and second year of treatment, and every 6 months in subsequent years to ensure early detection of any valvular or pericardial changes that may occur.

2.3.2 Psychiatric adverse events

In the course of UCB0942 development, 3 psychiatric SAEs (delirious syndrome, mania-like symptoms, and acute psychosis) have been reported in 2 healthy volunteers and 1 patient with resistant epilepsy, respectively. The events were transient, acute, and required admission to psychiatric care and antipsychotics. The events in healthy subjects occurred early after initiation of UCB0942, which was done without titration. In 1 of the subjects symptoms worsened upon abrupt drug discontinuation. The psychotic effect in the epilepsy subject emerged after dramatic improvement in seizures control and electroencephalographic activity a few weeks after start of UCB0942, suggesting "forced normalization" (Loganathan et al, 2015; Clemens, 2005). Dose reduction of UCB0942 and neuroleptic treatment resulted in complete resolution of psychosis within days, as the treatment with UCB0942 continued.

In the current study, subjects will have a psychiatric (BPRS) and cognitive (MMSE) assessment at study visits every 3 months for years 1, 2 and 3, and every 6 months for years 4 and 5. The CIWA-B will be performed at the LEPV (last visit prior to the Taper Period)/EDV, at the visit at the end of the Taper Period and at SFU1 and SFU2 (1 week and 30 days after administration of the final dose of UCB0942, respectively). In addition, to further reduce the risk that participating subjects develop psychiatric AEs, subjects with a history of psychosis, schizophrenia, bipolar disorder, or severe unipolar depression will be excluded from this study. Lastly, based on the fact that titration has been shown to reduce the incidence of other AEs and increase the general tolerability of UCB0942, titration may also reduce the risk of psychiatric AEs.

2.3.3 Drug-drug interactions

A drug-drug interaction study in subjects with epilepsy showed that carbamazepine – a strong CYP3A4 inducer – reduced UCB0942 plasma exposure by >85%. Therefore, subjects on carbamazepine or other strong CYP3A4 inducers (eg, phenytoin, phenobarbital, or primidone) will not be enrolled in this study because the plasma exposure may be too low to produce any therapeutic benefit.

Preclinical data indicate the potential involvement of CYP2C19 in the metabolism of UCB0942.While the contribution of CYP2C19 is still unclear regarding the degree to which it

contributes to the metabolism of UCB0942 or its metabolites, both strong inhibitors and inducers of CYP2C19 will also be prohibited. Additionally, in studies with human study participants, drug-drug interaction of UCB0942 (perpetrator) with CYP2C19 substrates (victims) was observed leading to increased levels of CYP2C19 substrates. Therefore, concomitant use of sensitive CYP2C19 substrates will be prohibited in EP0073. If subjects are already taking strong inducers or inhibitors or sensitive substrates of CYP2C19 prior to Amendment 3, they may continue to do so, but close monitoring should be implemented.

2.4 Rationale for this study

UCB believes that, based on the evidence of unprecedented superiority to other marketed AEDs across several preclinical models of epilepsy, UCB0942 may be of potential benefit with an acceptable risk/benefit profile in a high unmet medical need patient population, namely those who have highly drug-resistant focal epilepsy whose uncontrolled seizures constitute a substantial threat to their health and well-being.

The EP0069 multicenter, randomized, double-blind placebo-controlled, parallel-group study will make the first assessment of the safety and efficacy of UCB0942 in the adjunctive treatment of POS with or without secondary generalization in subjects with highly drug-resistant epilepsy despite optimal medical AED treatment.

For those subjects who benefit substantially from UCB0942 in EP0069, the current OLE study will provide an opportunity to continue UCB0942 treatment after a careful evaluation of the individual benefit-risk balance and with close monitoring of safety, tolerability and efficacy of long-term study treatment. As such, the purpose of the current study, EP0073, is to assess the long-term safety, tolerability, and efficacy associated with oral UCB0942 in subjects with highly drug-resistant focal epilepsy. Also, the effects of UCB0942 on the subject's quality of life will be explored.

3 STUDY OBJECTIVE(S)

3.1 Primary objective

- To evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 100mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy.

3.2 Secondary objectives

- To evaluate the long-term efficacy of UCB0942
- To evaluate the effects of UCB0942 on the subject's quality of life.

3.3 Exploratory objective

- To evaluate the plasma concentrations of UCB0942 and metabolites.

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variable

- Occurrence of AEs reported by the subject and/or caregiver or observed by the Investigator or clinical site staff beginning at the EV of the Evaluation Period during the EP0073 study

4.1.2 Other safety variables

- Changes from EP0069 baseline in laboratory tests (including hematology, blood chemistry, urinalysis) at each assessment during the EP0073 study
- Changes from EP0069 baseline in 12-lead ECG parameters at each assessment during the EP0073 study
- Changes from EP0069 baseline in psychiatric assessments as assessed with the BPRS at each assessment during the EP0073 study
- Changes from EP0069 baseline in memory or cognition as assessed with the MMSE at each assessment during the EP0073 study
- Changes in withdrawal symptoms using CIWA-B from the LEPV (last visit prior to the Taper Period), at each assessment during the Taper Period (visit at the end of the Taper Period) and during the SFU Period (visits at 1 week and 30 days after administration of the final dose of UCB0942) of the EP0073 study
- Changes from EP0069 baseline in vital sign parameters (pulse rate, BP, and RR) at each assessment during the EP0073 study
- Occurrence of a clinically concerning valvular or pericardial effusion change or other clinically significant abnormalities as identified by 2-dimensional Doppler echocardiography at each assessment during the EP0073 study
- Changes from EP0069 baseline in physical examination (including body weight) and neurological examination findings at each assessment during the EP0073 study

4.2 Efficacy variables

In both this study and EP0069 only POS of type IA1, IB, and IC and not non-motor IA2, IA3 or IA4 seizures will be counted for the assessment of seizure frequency and responder rate. For assessment of seizure-free rate and days, all seizure types will be considered.

4.2.1 Primary efficacy variable

- The primary efficacy variable is the 75%RR by 3-month intervals over the Evaluation Period. A 75% responder is defined as a subject with a ≥75% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069.

4.2.2 Secondary efficacy variables

- Median POS frequency per 28 days by 3-month intervals over the Evaluation Period of the EP0073 study.

- Median POS frequency per 28 days by seizure type by 3-month intervals over the Evaluation Period of the EP0073 study.
- Percent reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069 by 3-month intervals over the Evaluation Period of the EP0073 study.
- The 50% responder rate (50%) RR by 3-month intervals over the Evaluation Period of the EP0073 study. A 50% responder is defined as a subject with a ≥50% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069.
- Percentage of seizure-free days by 3-month intervals over the Evaluation Period.
- Seizure-free rate by 3-month intervals over the Evaluation Period.
- Changes in QOLIE-31-P scores from V3 of EP0069 through the assessment of the Evaluation Period.

4.3 Exploratory pharmacokinetic variable

- Plasma concentrations of UCB0942 and metabolites during the first 13 months of treatment in EP0073.

5 STUDY DESIGN

5.1 Study description

This is an OLE study that will run throughout the clinical development period of UCB0942 and will continue for approximately 5 years or until either until a marketing authorization is granted by any health authority for the adjunctive treatment for POS in adult subjects with highly drug-resistant focal epilepsy, or until UCB decides to close the study.

Subjects who experience substantial benefit from UCB0942 with acceptable tolerability in EP0069 may have the opportunity to continue UCB0942 treatment in this OLE study. The decision to enter this study must be made by the Investigator in consultation with the subject and his/her caregiver. The Investigator's decision must take into account the benefit experienced and the potential risks of long-term exposure to UCB0942, as well as the potential benefit and risks of other treatment options available.

A DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the IMP. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, or termination of the clinical study.

The study will consist of:

- A 2-week Screening Period from V13 to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study. At this visit, informed consent will be signed and

inclusion and exclusion criteria (from the current OLE study) will be checked. The verbatim of the attained benefits of treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be captured as narratives and filled in by the Investigator or site personnel. During the Screening Period, the Investigator will also provide a statement and a brief justification of the benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942. These narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be maintained as source documents and will be reviewed by the DMC.

- An Evaluation Period of up to approximately 5 years, which will start with V2, the EV, which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Eligible subjects will enter EP0073 before the planned dose tapering in EP0069. Subjects will be issued and return seizure diaries during each visit. Subjects must be educated to record all types of seizures that occur, any illness or injury, and all study medication intake in their seizure diary and be educated to complete their diary entries after each seizure or at least once a day. Throughout the study, the Investigator also will be requested to periodically re-assess and re-confirm that the benefit-risk ratio for the subject on long-term treatment with the IMP, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options, justifies continuation in the study. Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at the scheduled time points presented in Table 5–2.

  First year:

  In the first month of EP0073, subjects will have 2 TCs (M1-Wk1 [TC1] and M1-Wk3 [TC2]) and 1 clinic visit (M1-Wk2 [V3]). During the 2 TCs, the site personnel will review changes in concomitant medications (including AEDs), confirm whether the subject experienced any AEs/SAEs, and ensure that subjects are compliant with their study medication dosing schedule as outlined in the protocol.

  During the second, third and fourth months, subjects will visit the clinic at M2 (V4, MEV), M3 (V5, FEV), and M4 (V6, MEV).

  Subjects will return to the clinic every 3 months for the remainder of the first year with FEV alternating with MEV: M7 (V7, FEV) and M10 (V8, MEV).

  Second and third year:

  For the second and third years, subjects will have clinic visits every 3 months, with MEVs alternating with FEVs/YEVs, beginning with M13 (V9, YEV).

  Fourth and fifth year:

  For subjects who continue to participate in EP0073 beyond the 3-year period, the subjects will have a clinic visit every 6 months with YEVs alternating FEVs.

- A Taper Period starting at the LEPV of the Evaluation Period; during the Taper Period, subjects will start to gradually decrease their dose of UCB0942. The Taper Period is planned to be 3 weeks; however, a faster taper schedule than the suggested 3 weeks may be

implemented if medically necessary. A slower taper schedule of up to 6 weeks may be implemented as per the Investigator's medical judgment.

- A SFU Period; subjects must return to the clinic 1 week after administration of the final dose of UCB0942 (SFU1). A FV will be scheduled 30 days after administration of the final dose of UCB0942 (SFU2).

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. Exceptions may be allowed after consultation with the PRA Medical Monitor. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction. For details, please refer to Section 7.2.

If at any time, the subject and/or the Investigator decide to discontinue UCB0942, the subject should return for an EDV and gradually decrease their dose of UCB0942.

At the end of the Evaluation Period, subjects will return for a LEPV and will start to gradually decrease their dose of UCB0942. Subjects must return to the clinic for a visit at the end of the Taper Period. A suggested 3-week taper schedule and further details on dose tapering are given in Section 7.2.

The CIWA-B will be used to monitor for withdrawal signs/symptoms during the Taper and Safety Follow-Up Periods.

5.1.1 Study duration per subject

For each subject, the study will last from study entry for approximately 5 years or until either a marketing authorization is granted by any health authority for the adjunctive treatment for POS in adult subjects with highly drug-resistant focal epilepsy, or until UCB decides to close the study.

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

5.1.2 Planned number of subjects and sites

It is estimated that approximately 40 subjects who completed EP0069 will be included in multiple sites in Europe.

5.1.3 Anticipated regions and countries

The study is planned to be performed in The Netherlands, Belgium, Bulgaria, and Germany. Other countries in the European Union can be added if deemed necessary by the Sponsor.

5.2 Visit schedule

The visit schedule is presented in Table 5–1.

Visit windows will be as follows: ±3 days for the 1-month visit intervals, ±4 days for the 3-month visit intervals, ±1 week for the 5- or 6-month visit intervals, and +7 days for SFU2.

Table 5–1: Study visit schedule

Month	Visit	Type of visit
First study year		
M0	V1 (V13 of EP0069)	Screening Visit
M1	V2 (V15 of EP0069)	EV
M1-Wk1	TC1	TC
M1-Wk2	V3	MEV
M1-Wk3	TC2	TC
M1-Wk4	-[a]	-
M2	V4	MEV
M3	V5	FEV
M4	V6	MEV
M5	-	-
M6	-	-
M7	V7	FEV
M8	-	-
M9	-	-
M10	V8	MEV
M11	-	-
M12	-	-
Second study year		
M13	V9	YEV
M16	V10	MEV
M19	V11	FEV

Table 5–1: Study visit schedule

Month	Visit	Type of visit
M22	V12	MEV
Third study year		
M25	V13	YEV
M28	V14	MEV
M31	V15	FEV
M34	V16	MEV
Fourth study year		
M37	V17	YEV
M43	V18	FEV
Fifth study year		
M49	V19	YEV
M55	V20	FEV
M58	V21	YEV and LEPV/EDV
Taper and SFU Periods[b]		
Taper Period	V22	End of Taper Visit
SFU1	V23	SFU at 1 week after final dose
SFU2	V24	SFU at 30 days after final dose (FV)

EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; LEPV=Last Evaluation Period Visit; M=Month; MEV=Minimal Evaluation Visit; SFU=Safety Follow-Up; TC=Telephone Call; V=Visit; Wk=Week; YEV=Yearly Evaluation Visit

[a] The "-" denotes that no visit is scheduled in that month

[b] Taper and SFU Periods to start with EDV or LEPV.

Please note that unscheduled visits or telephone contacts may be performed at any time after V1 at the discretion of the Investigator.

An unscheduled visit may be performed, for example, when the UCB0942 dose is increased or decreased. The following assessments will be required during this visit:

- Recording of AEs
- Recording of concomitant medications
- Contact interactive response technology (IRT; in case of increase or decrease in UCB0942 dose)

In addition to the required assessments listed above, further assessments can be completed at the unscheduled visit as needed and may include 12-lead ECG, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS), BPRS, laboratory tests (including urine pregnancy test [for women of childbearing potential]), etc. Study medication may be dispensed, if required.

An unscheduled visit or a telephone contact is recommended to follow up with the evolution of subject's condition subsequent to the increase or decrease of the UCB0942 dose.

Reasons for any unscheduled visits or telephone contacts should be documented.

5.3 Schedule of study assessments

The schedule of study assessments is presented in Table 5–2.

Table 5–2: Schedule of study assessments

Assessments	Screening Period		Evaluation Period				Taper Period[a]	SFU Period	
	Screening Visit	EV	Telephone Calls	FEV	MEV	YEV and LEPV (V21)/EDV	End of Taper Visit	SFU1 at 1 week	SFU2 at 30 days/ FV
Visit	**V1 (V13 of EP0069)**	**V2 (V15 of EP0069)**	**TC1, TC2**	**V5, V7, V11, V15, V18, V20**	**V3, V4, V6, V8, V10, V12, V14, V16**	**V9, V13, V17, V19, V21**	**V22**	**V23**	**V24**
Week/Month	**M0**	**M1**	**M1-Wk1, M1-Wk3**	**M3, M7, M19, M31, M43, M55**	**M1-Wk2, M2, M4, M10, M16, M22, M28, M34**	**M13, M25, M37, M49, M58**	**NA**	**NA**	**NA**
Written informed consent	X								
Demographic data[b]		X							
Verification of inclusion/exclusion criteria[c]	X	X							
Withdrawal criteria			X	X	X	X			
General medical/ procedure history[b]		X							
Complete physical examination		X		X		X			X
Brief physical examination					X		X	X	
Complete neurological examination		X		X		X	X	X	X
Brief neurological examination					X				
BMI		X							

Table 5–2: Schedule of study assessments

Assessments	Screening Period		Evaluation Period				Taper Period[a]	SFU Period	
	Screening Visit	EV	Telephone Calls	FEV	MEV	YEV and LEPV (V21)/EDV	End of Taper Visit	SFU1 at 1 week	SFU2 at 30 days/ FV
Visit	**V1 (V13 of EP0069)**	**V2 (V15 of EP0069)**	**TC1, TC2**	**V5, V7, V11, V15, V18, V20**	**V3, V4, V6, V8, V10, V12, V14, V16**	**V9, V13, V17, V19, V21**	**V22**	**V23**	**V24**
Week/Month	**M0**	**M1**	**M1-Wk1, M1-Wk3**	**M3, M7, M19, M31, M43, M55**	**M1-Wk2, M2, M4, M10, M16, M22, M28, M34**	**M13, M25, M37, M49, M58**	**NA**	**NA**	**NA**
Vital signs (BP, pulse, and RR) and body weight		X		X	X	X	X	X	X
Echocardiogram		X		X	X[d]	X			X
12-lead ECG[e]		X		X		X			X
Concomitant medications		X	X	X	X	X	X	X	X
Concomitant AEDs		X	X	X	X	X	X	X	X
Screening for drug and alcohol use[f]		X		X		X			
Laboratory tests									
Chemistry/hematology		X		X		X			X
Urinalysis		X		X		X			X
Serum pregnancy test[g]		X							X
Urine pregnancy test[g]				X	X	X	X	X	
C-SSRS (since last visit)		X		X	X	X	X	X	X
QOLIE-31-P[h]				X		X			

Table 5–2: Schedule of study assessments

Assessments	Screening Period		Evaluation Period				Taper Period[a]	SFU Period	
	Screening Visit	EV	Telephone Calls	FEV	MEV	YEV and LEPV (V21)/EDV	End of Taper Visit	SFU1 at 1 week	SFU2 at 30 days/ FV
Visit	**V1 (V13 of EP0069)**	**V2 (V15 of EP0069)**	**TC1, TC2**	**V5, V7, V11, V15, V18, V20**	**V3, V4, V6, V8, V10, V12, V14, V16**	**V9, V13, V17, V19, V21**	**V22**	**V23**	**V24**
Week/Month	**M0**	**M1**	**M1-Wk1, M1-Wk3**	**M3, M7, M19, M31, M43, M55**	**M1-Wk2, M2, M4, M10, M16, M22, M28, M34**	**M13, M25, M37, M49, M58**	**NA**	**NA**	**NA**
Narratives of benefit and benefit-risk assessment[i]		X		X	X	X			X
BPRS		X		X	X	X			X
MMSE		X		X	X	X			X
CIWA-B						X[j]	X	X	X
Sample for UCB0942, [redacted], and plasma concentrations[k]				X	X	X			
Call IRT		X		X	X	X	X		
Dispense subject diary		X		X	X	X	X	X	
Subject diary return				X	X	X	X	X	X
Dispense study medication		X		X	X	X			
Study medication return				X	X	X	X		
Adverse event reporting		X	X	X	X	X	X	X	X

Table 5–2: Schedule of study assessments

Assessments	Screening Period		Evaluation Period				Taper Period[a]	SFU Period	
	Screening Visit	EV	Telephone Calls	FEV	MEV	YEV and LEPV (V21)/EDV	End of Taper Visit	SFU1 at 1 week	SFU2 at 30 days/ FV
Visit	V1 (V13 of EP0069)	V2 (V15 of EP0069)	TC1, TC2	V5, V7, V11, V15, V18, V20	V3, V4, V6, V8, V10, V12, V14, V16	V9, V13, V17, V19, V21	V22	V23	V24
Week/Month	M0	M1	M1-Wk1, M1-Wk3	M3, M7, M19, M31, M43, M55	M1-Wk2, M2, M4, M10, M16, M22, M28, M34	M13, M25, M37, M49, M58	NA	NA	NA

AED=antiepileptic drug; BMI=body mass index; BP=blood pressure; BPRS=Brief Psychiatric Rating Scale; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; IRT=interactive response technology; LEPV=Last Evaluation Period Visit; M=Month; MEV=Minimal Evaluation Visit; MMSE=Mini-Mental State Examination; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; RR=respiratory rate; SFU=Safety Follow-Up; TC=Telephone Call; V=Visit; Wk=Week; YEV=Yearly Evaluation Visit

[a] During the Taper Period, dose tapering will be done through TCs; a clinical visit will be performed at end of Taper Period, ie, V22. The Taper Period is planned to be 3 weeks; however, a faster taper schedule than the suggested 3 weeks may be implemented if medically necessary. A slower taper schedule of up to 6 weeks may be implemented as per the Investigator's medical judgment.

[b] Demographic and general medical/procedure history data will be obtained from EP0069 and updated if necessary. Information regarding surgical evaluation, working status, caregiver support, and supervision should be collected within 30 days after Protocol Amendment 2 is approved.

[c] From EP0073 study.

[d] No echocardiogram will be done at V3, V14, and V16.

[e] Standard 12-lead ECGs will be recorded prior to laboratory tests.

[f] The drug screen will include amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, methadone, opiates, and alcohol. Use of AED from one of the classes mentioned will be allowed if allowed by inclusion and exclusion criteria.

[g] For females of childbearing potential only.

[h] The QOLIE-31-P will be completed by all subjects who are not mentally impaired, prior to any other study procedures at the visit.

[i] Narratives of benefit and benefit-risk assessment can be completed any time during the Screening Period after obtaining informed consent and before eligibility check at V2.

[j] During the Evaluation Period, the CIWA-B will be performed at V21 only (LEPV) or at EDV.

[k] Obtain blood samples for measurement of plasma concentration of UCB0942 and metabolites at V3, V4, V5, V6, V7, V8 and V9.

5.4 Rationale for study design and selection of dose

This OLE study will assess the long-term safety and efficacy of UCB0942 in the adjunctive treatment of seizures with or without secondary generalization in adult subjects with highly drug-resistant focal epilepsy. Also, the the effects of UCB0942 on the subject's quality of life will be explored.

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. In EP0073 doses can range from 50mg bid to 400mg bid. The highest UCB0942 dose of 400mg bid used in this study has been chosen because it is the maximum tolerated dose in Phase 1 studies. This dose is expected to:

1. Achieve exposures similar to those that show unprecedented efficacy in the rat amygdala kindling model of drug-resistant focal epilepsy,
2. Achieve full and constant SV2 occupancy based on modeling predictions, and
3. Achieve 10 to 15% occupancy of the cBZR site on the GABA-A receptor.

Throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration unless agreed by the PRA Medical Monitor.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. A written Informed Consent form approved by the IEC is signed and dated by the subject, after the Investigator assesses whether the subject is able to understand the potential risks and benefits of participating in the study.
2. Subject and/or caregiver is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.
3. Subject must have completed V13 of the Outpatient Maintenance Period of EP0069 to be eligible for enrollment into EP0073.
4. In EP0069, the subject demonstrated a reduction in frequency and/or severity of seizures as compared to baseline that is considered clinically significant by the Investigator and significant by the subject.
5. In EP0069, the subject experiences substantial benefit from UCB0942 with acceptable tolerability according to the subject and Investigator.
6. No tolerability issues that can outweigh attained benefits, in the opinion of the Investigator.

7. Female subjects of nonchildbearing potential (premenarcheal, postmenopausal for at least 2 years, bilateral oophorectomy or tubal ligation, and complete hysterectomy) are eligible. Female subjects of childbearing potential are eligible if they use medically accepted contraceptive methods. Oral or depot contraceptive treatment used with an additional barrier contraception method, monogamous relationship with vasectomized or female partner, or double-barrier contraception are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. Abstinence will be considered as an acceptable method of contraception if the Investigator can document that the subject agrees to be compliant when it is in line with the preferred and usual lifestyle of the subject.
8. Male subject confirms that, during the study period and for a period of 3 months after the final dose, when having sexual intercourse with a woman of childbearing potential, he will use a barrier contraceptive (eg, condom).

6.2 Exclusion criteria

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

1. Subject has any severe medical, neurological, or psychiatric condition, or laboratory value which may have an impact on the safety of the subject.
2. 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.
3. Subject has developed a known hypersensitivity to any components of the IMP as stated in this protocol during participation in EP0069.
4. Subject has poor compliance with the visit schedule of medication intake in the EP0069 study according to the Investigator's judgment.
5. Subject plans participation in any other clinical study of another investigational drug or device while participating in this study (with the exception of participating in the EP0069 study).
6. Subject is a woman who is pregnant or lactating.
7. Subject has taken other (non-AED) prescription, non-prescription, dietary (eg, grapefruit or passion fruit), or herbal products that are potent inducers or inhibitors of the CYP3A4 pathway for 2 weeks (or 5 half-lives whichever is longer) prior to study entry.
8. Subject has an abnormality in the 12-lead ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any subject with any of the following findings will be excluded:
   - Prolonged QTc (Bazett's, machine-read) interval defined as >450ms for males and >470ms for females
   - Bundle branch blocks and other conduction abnormalities other than mild first degree atrioventricular block (defined as PR interval ≥220ms)

- Irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats
- In the judgment of the Investigator, T-wave configurations are not of sufficient quality for assessing QT interval duration

9. Subject has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
10. Subject has a clinically significant abnormality on echocardiography at the EV (V2) of EP0073.
11. Subject has any medical condition which, in the Investigator's opinion, warrants exclusion.
12. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome) at the EV (V2) of EP0073 (V15 of EP0069). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For enrolled subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening (ie, the value is >ULN but ≤2xULN at the EV [V2] of EP0073), repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

6.3 Withdrawal criteria

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

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

Investigators should contact the PRA Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

Subjects must be withdrawn from the study if any of the following events occur:

1. Withdrawal for safety reasons by the Investigator and/or when the benefit-risk ratio of the IMP treatment is 0 to 4 (on a scale from 0 to 10), indicating the risks outweigh the benefits.

2. Subject is suspected of having a serious multiorgan hypersensitivity reaction. Serious suspected multiorgan hypersensitivity cases may be identified and reported to the Sponsor by the Investigator using the following algorithm:
   - An AE or laboratory value (as defined below) suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least one of the following: fever, rash, lymphadenopathy, or eosinophilia.
   - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
   - Eosinophils percentage ≥10%
   - Eosinophils absolute ≥0.5G/L
   - Neutrophils absolute <1.5G/L
   - Platelets absolute ≤100G/L
3. Subject cannot tolerate the minimum UCB0942 dose of 50mg bid (100mg/day).
4. Subject and/or Investigator does not think that the investigational drug is effective (ie, lack or loss of efficacy).
5. Subject is lost to follow up.
6. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
7. Subject takes prohibited concomitant medications:
   - Carbamazepine, phenytoin, phenobarbital, primidone, or other AEDs that are strong CYP3A4 inducers
   - Benzodiazepines taken >3 times per week
   - Zolpidem, zaleplon, or zopiclone taken >3 times per week
   - Tiagabine
   - Felbamate
   - Vigabatrin
   - Strong non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)
8. Subject withdraws his/her consent.
9. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
10. The Sponsor or a regulatory agency requests withdrawal of the subject.

11. Subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk of continuing the subject in the study/on study medication. Subject has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
12. A prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the Investigator as serious enough to warrant discontinuation from the study.
13. An ECG shows an absolute value for QT corrected for heart rate using Bazett's formula (QTcB) or QT corrected for heart rate using Fridericia's formula (QTcF) ≥500ms or ≥60ms above baseline.
14. Subject develops second- or third-degree atrioventricular block or another clinically relevant change in ECG as determined by the Investigator.
15. Subject has an abnormality on the echocardiogram that is clinically concerning or that worsens over time.
16. For subjects developing psychiatric/mood/behavioral signs or disturbances (see examples in list below) that are clinically concerning or that worsen over time, the study drug dose should be gradually reduced and, if symptoms persist, withdrawal from study should be recommended. Subjects should be referred to a mental health professional, and continuation of the study treatment should only be allowed with the approval and under close oversight of the mental health specialist, and upon confirmation of the positive benefit-risk by the Investigator.
    a. Auditory or visual hallucinations
    b. Delusions / paranoia / grandeur
    c. Disorganized thought process
    d. Agitation / aggression / apathy
    e. Dysphoria / depression / mood lability / euphoria
    f. Disinhibition
    g. Cognitive changes / memory impairment / delirium
    h. Aberrant motor behavior

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 11.6.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

The IMP is supplied as white, film-coated tablets in strengths of 25mg, 100mg, and 200mg.

7.2 Treatments to be administered

Subjects being enrolled in the current study from EP0069 will continue their dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration unless agreed by the PRA Medical Monitor. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. The PRA Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction, if the concomitant medication has been approved for focal seizures by the health authority of the subject's country of residence, taking the drug-to-drug interactions profile of UCB0942 into account. New AEDs (with the exception of AEDs listed in the prohibited medication section, Section 7.8.2) should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of UCB0942.

If at any time, the subject and/or the Investigator decide to discontinue UCB0942, the subject should return for an EDV and gradually decrease their dose of UCB0942 as described below.

At the end of the Evaluation Period, subjects will return for a LEPV and will start to gradually decrease their dose of UCB0942. During the Taper Period, sites should contact subjects by telephone to discuss their dose adjustments. Subjects must return to the clinic for a visit at the end of the Taper Period. A suggested 3-week taper schedule is described in Table 7–1.

Table 7–1: Three-week taper schedule for UCB0942

Daily dose at LEPV/EDV (mg/day)	Taper Week 1 (mg/day)	Taper Week 2 (mg/day)	Taper Week 3 (mg/day)
600 and 800	500[a]	300[a]	100
400	300[a]	100	-

Table 7–1: Three-week taper schedule for UCB0942

Daily dose at LEPV/EDV (mg/day)	Taper Week 1 (mg/day)	Taper Week 2 (mg/day)	Taper Week 3 (mg/day)
200	100	-	-
100	-	-	-

EDV=Early Discontinuation Visit; LEPV=Last Evaluation Period Visit

[a] It is recommended to divide uneven doses with a lower dose in the morning and a higher dose in the evening to the discretion of the Investigator.

A faster taper schedule than the suggested 3 weeks should only be implemented if medically necessary. A slower taper schedule of up to 6 weeks may be implemented as per the Investigator's medical judgment. During the Taper Period, the dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart.

During the Taper Period, the Investigator is allowed to add any additional AED(s) following the Investigator's medical judgment (with the exception of AEDs listed in the prohibited medication section, Section 7.8.2).

The CIWA-B will be used to monitor for withdrawal signs/symptoms during the Taper and Safety Follow-Up Periods.

7.3 Packaging

UCB0942 tablets are manufactured, packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way to protect the IMP from deterioration during transport and storage. Packaging details are included in the IMP Handling Manual.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of UCB0942 at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (ie, every working day), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions and IMP information contained in the IMP Handling Manual. The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

7.6 Drug accountability

A Drug Accountability form will be used to record UCB0942 dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any UCB0942 lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of UCB0942 until returned or destroyed at the site per local procedures.

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

The Investigator must ensure that UCB0942 is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers), partially used and unused UCB0942 containers must be reconciled and either be destroyed at the site per local procedures or returned to UCB (or designee), preferably in their original package. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

At each visit after UCB0942 is dispensed, subjects must return all unused UCB0942 and empty UCB0942 containers. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant (defined as less than 75% or more than 125% compliant with the dosage schedule), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from the study.

Timely completion of the subject diary is essential for evaluation of safety, efficacy, and study medication intake. A caregiver is allowed to help the subject with the completion of the subject diary. Subject diary completion will be evaluated at each visit.

7.8 Concomitant medication(s)/treatment(s)

7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- All subjects will enter EP0073 using their current AED regimen. Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject. Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction. Changes in AEDs should be discussed with the PRA Medical Monitor on an individual and case-by-case basis.
- Oxcarbazepine, eslicarbazepine.

- Benzodiazepines (as a rescue medication ≤3 doses within 7 days).
- Other medication, not mentioned as prohibited.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study (this is not a complete list of prohibited medications):

- Carbamazepine, phenytoin, phenobarbital, primidone, or other AEDs that are strong CYP3A4 inducers
- Benzodiazepines taken >3 times per week (ie, >3 doses within 7 days)
- Zolpidem, zaleplon, or zopiclone taken >3 times per week
- Tiagabine
- Felbamate
- Vigabatrin
- Strong non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

The following medications* should not be administered concomitantly with UCB0942. However, if subjects are already taking these medications prior to Amendment 3, they may continue to do so, but close monitoring should be implemented.

- Strong CYP2C19 inhibitors (eg, fluconazole, fluoxetine, fluvoxamine, and ticlopidine)
- Strong CYP2C19 inducers (eg, including rifampicin and ritonavir)
- CYP2C19 sensitive substrates (eg, s-mephenytoin and omeprazole)

*For more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers.

7.8.3 Rescue medication

Benzodiazepines can be used as rescue medication (≤3 doses within 7 days).

7.9 Blinding

This is an OLE study so no blinding is required. A DMC (see Section 13.8) will review blinded data up until final unblinding from EP0069 and data from the OLE EP0073 studies to provide an ongoing evaluation of the safety signals and the benefit-risk balance for the study subjects.

7.10 Randomization and numbering of subjects

Randomization is not applicable in the current study. Subjects will be identified with the subject number they received in the EP0069 study.

An IRT will generate individual assignments for subject kits of UCB0942, as appropriate, according to the visit schedule and the dose the subject should receive.

The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject.

8 STUDY PROCEDURES BY VISIT

Details of the study assessments to be performed at specific time points prior to and after UCB0942 administration are provided in Table 5–2, and an outline of all assessments performed is provided in the sections below.

Visit windows will be as follows: ±3 days for the 1-month visit intervals, ±4 days for the 3-month visit intervals, ±1 week for the 5- or 6-month visit intervals, and +7 days for SFU2.

8.1 Screening Period

The Screening Visit, V1, is the same as V13 (Day OP43) of the 8-week Outpatient Maintenance Period of EP0069. At the Screening Visit the following items will be covered:

- Written informed consent
- Review of inclusion/exclusion criteria (from EP0073)
- Narratives of benefit and benefit-risk assessment

8.2 Evaluation Period

8.2.1 Entry Visit

The EV, V2, is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Data collected at V15 in EP0069 must also be recorded at V2 in the EP0073 eCRF. During the EV the following assessments will be performed:

- Review demographic, medical, medication, and procedural data from EP0069 and update where necessary; collect information regarding surgical evaluation, working status, caregiver support, and supervision within 30 days after Protocol Amendment 2 is approved.
- Concomitant AEDs and non-AEDs; any ongoing concomitant medications from EP0069 must also be recorded on the EP0073 eCRF. Details are provided in the eCRF Completion Guidelines.
- Review of inclusion/exclusion criteria (from EP0073)
- Calculation of body mass index (BMI)
- Complete physical examination
- Complete neurological examination
- Vital signs (BP, pulse, and RR) and body weight
- Echocardiogram (this can be done on another day within 1 week from the EV)
- 12-lead ECG (prior to laboratory tests)
- Drug and alcohol screening
- Clinical laboratory (clinical chemistry, hematology, and urinalysis)
- Serum pregnancy test (female subjects of childbearing potential only)

- C-SSRS (since last visit)
- Narratives of benefit and benefit-risk assessment (if not performed at V1)
- BPRS
- MMSE
- Call IRT
- Dispense subject diary
- Dispense study medication
- AE reporting

8.2.2 Telephone Calls

The subject will be contacted by telephone in Week 1 (TC1) and Week 3 (TC2). During the Telephone Call the following items will be covered:

- Withdrawal criteria
- Concomitant medication recording
- Concomitant AEDs
- AE reporting

8.2.3 Minimal Evaluation Visit

The MEVs are planned in M1-Wk2 (V3), M2 (V4), M4 (V6), M10 (V8), M16 (V10), M22 (V12), M28 (V14) and M34 (V16). During the MEVs the following assessments will be performed:

- Withdrawal criteria
- Brief physical examination
- Brief neurological examination
- Vital signs (BP, pulse, and RR) and weight
- Echocardiogram (not at V3, V14, and V16)
- Concomitant medication recording
- Concomitant AEDs
- Urine pregnancy test (female subjects of childbearing potential only)
- C-SSRS (since last visit)
- Narratives of benefit and benefit-risk assessment
- BPRS
- MMSE
- Blood sample for measurement of plasma concentration of UCB0942 and metabolites (only at V3, V4, V6, and V8)

- Call IRT
- Dispense and return subject diary
- Dispense and return study medication
- AE reporting

8.2.4 Full Evaluation Visit

The FEVs are planned in M3 (V5), M7 (V7), M19 (V11), M31 (V15), M43 (V18), and M55 (V20). During the FEVs the following assessments will be performed:

- Withdrawal criteria
- Complete physical examination
- Complete neurological examination
- Vital signs (BP, pulse, and RR) and weight
- Echocardiogram
- 12-lead ECG (prior to laboratory tests)
- Concomitant medication recording
- Concomitant AEDs
- Drug and alcohol screening
- Clinical laboratory (clinical chemistry, hematology, and urinalysis)
- Urine pregnancy test (female subjects of childbearing potential only)
- C-SSRS (since last visit)
- QOLIE-31-P (will be completed by all subjects who are not mentally impaired, prior to any other study procedures at the visit)
- Narratives of benefit and benefit-risk assessment
- BPRS
- MMSE
- Blood sample for measurement of plasma concentration of UCB0942 and metabolites (only at V5 and V7)
- Call IRT
- Dispense and return subject diary
- Dispense and return study medication
- AE reporting

8.2.5 Yearly Evaluation Visit and Early Discontinuation Visit

The YEVs are planned in M13 (V9), M25 (V13), M37 (V17), M49 (V19), and M58 (V21; also LEPV).

During the YEVs, and also during the EDV, the following assessments will be performed:

- Withdrawal criteria
- Complete physical examination
- Complete neurological examination
- Vital signs (BP, pulse, and RR) and weight
- Echocardiogram
- 12-lead ECG (prior to laboratory tests)
- Concomitant medication recording
- Concomitant AEDs
- Drug and alcohol screening
- Clinical laboratory (clinical chemistry, hematology, urinalysis)
- Urine pregnancy test (female subjects of childbearing potential only)
- C-SSRS (since last visit)
- QOLIE-31-P (will be completed by all subjects who are not mentally impaired, prior to any other study procedures at the visit)
- Narratives of benefit and benefit-risk assessment
- BPRS
- MMSE
- CIWA-B (at V21 only [LEPV] or at EDV)
- Blood sample for measurement of plasma concentration of UCB0942 and metabolites (only at V9)
- Call IRT
- Dispense and return subject diary
- Dispense and return study medication
- AE reporting

For the EDV, if no visit can be scheduled, all efforts should be taken to contact the subject and obtain at least the following information:

- Concomitant medication recording
- AE reporting

8.3 Taper Period

An End of Taper Visit to the clinic is planned (V22) during which the following assessments will be performed:

- Brief physical examination

- Complete neurological examination
- Vital signs (BP, pulse, and RR) and weight
- Concomitant medication recording
- Concomitant AEDs
- Urine pregnancy test (female subjects of childbearing potential only)
- C-SSRS (since last visit)
- CIWA-B
- Call IRT
- Dispense and return subject diary
- Return study medication
- AE reporting

8.4 Safety Follow-Up Period

8.4.1 Safety Follow-Up Visit 1

Subjects must return to the clinic 1 week after administration of the final dose of study medication (SFU1). During SFU1, the following assessments will be performed:

- Brief physical examination
- Complete neurological examination
- Vital signs (BP, pulse, and RR) and body weight
- Concomitant medication recording
- Concomitant AEDs
- Urine pregnancy test (female subjects of childbearing potential only)
- C-SSRS (since last visit)
- CIWA-B
- Dispense and return subject diary
- AE reporting

8.4.2 Safety Follow-Up Visit 2

A FV will be scheduled 30 days after administration of the final dose of UCB0942 (SFU2). During SFU2, the following assessments will be performed:

- Complete physical examination
- Complete neurological examination
- Vital signs (BP, pulse, and RR) and body weight
- Echocardiogram

- 12-lead ECG (prior to laboratory tests)
- Concomitant medication recording
- Concomitant AEDs
- Clinical laboratory (clinical chemistry, hematology, and urinalysis)
- Serum pregnancy test (female subjects of childbearing potential only)
- C-SSRS (since last visit)
- Narratives of benefit and benefit-risk assessment
- BPRS
- MMSE
- CIWA-B
- Return subject diary
- AE reporting

8.5 Unscheduled Visit/Telephone Contact

Please note that unscheduled visits or telephone contacts may be performed at any time after V1 at the discretion of the Investigator.

An unscheduled visit may be performed, for example, when the UCB0942 dose is increased or decreased. The following assessments will be required during this visit:

- Recording of AEs
- Recording of concomitant medications
- Contact IRT (in case of increase or decrease in UCB0942 dose)

In addition to the required assessments listed above, further assessments can be completed at the unscheduled visit as needed and may include 12-lead ECG, vital signs, C-SSRS, BPRS, narratives of benefit and benefit-risk assessment, laboratory tests (including urine pregnancy test [for women of childbearing potential]), etc. Study medication may be dispensed, if required.

An unscheduled visit or a telephone contact is recommended to follow up with the evolution of subject's condition subsequent to the increase or decrease of the UCB0942 dose.

Reasons for any unscheduled visits or telephone contacts should be documented.

9 ASSESSMENT OF EFFICACY

The efficacy variables are described in detail in Section 4.2.

9.1 Seizure frequency

During the study, subjects will keep diaries to record daily seizure activity from the EV until the end of study participation. Subjects should be reminded to bring their diaries with them to each clinic visit.

The written information will be discussed with the subjects at each visit in order to ensure completeness and accuracy. As a result of the discussion, the Investigator will assess the seizures according to the International League Against Epilepsy codes and record the seizure types and frequency in the eCRF; he/she will also confirm the presence of AEs if applicable.

Subjects should record all types of seizures that occur in their diary and be educated to complete their diary entries after each seizure or at least once a day (eg, when taking evening tablets). A caregiver can assist in completing the diary if necessary. Substantial noncompliance with diary completion (seizure recording) may result in subject discontinuation from the study at any time by the Investigator or the Sponsor; see Section 6.3.

The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

9.2 Quality of Life Inventory in Epilepsy-31-P

The QOLIE-31-P assesses subject functioning and health-related quality of life.

The QOLIE-31-P is an adaptation of the original QOLIE 31 instrument (Cramer and Van Hammée, 1998) that includes 30 items grouped into 7 multi item subscales (Seizure Worry [5 items], Overall Quality of Life [2 items], Emotional Well-being [5 items], Energy/Fatigue [4 items], Cognitive Functioning [6 items], Medication Effects [3 items], and Daily Activities/Social Functioning [5 items]) and 1 health status item.

In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items assessing the degree of "distress" associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

The QOLIE-31-P will be completed at the scheduled time points presented in Table 5–2. At the very beginning of the visit, the QOLIE-31-P will be provided to all subjects. The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the QOLIE-31-P will be covered in the Study Manual.

10 ASSESSMENT OF PHARMACOKINETICS

10.1 Sampling procedures

Blood samples for PK will be obtained at the scheduled time points presented in Table 5–2.

Exact sampling times will be recorded in the eCRF.

Detailed information on the collection, storage, preparation, and shipping of samples will be presented in a Laboratory Manual.

10.2 Bioanalytical methods

Plasma concentrations of UCB0942 and metabolites [redacted] and [redacted] will be determined using validated bioanalytical methods.

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Prospective Outpatient Baseline Period from the EP0069 study.

11.1.2 Procedures for reporting and recording adverse events

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

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

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

11.1.3 Description of adverse events

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

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

11.1.4 Follow up of adverse events

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

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the

Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her IMP.

In case of cardiac treatment-emergent AEs (TEAEs) associated with echocardiographic findings, the subject must be withdrawn from the study if the finding is clinically concerning or worsens over time, and the following should be completed:

- The subject should return for an EDV
- The subject should immediately stop the intake of UCB0942 or be down titrated as instructed at the EDV
- Safety Follow-up Visits should be scheduled 1 week and 30 days after the subject has discontinued UCB0942

These TEAEs should be followed up at least 6 months or until they have resolved, have a stable sequelae, or the subject is lost to follow up.

11.1.5 Rule for repetition of an adverse event

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

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

11.1.6 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Patient Safety (PS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of UCB0942 or be down titrated as instructed at the EDV.
- Safety Follow-Up Visits should be scheduled 1 week and 30 days after the subject has discontinued UCB0942.

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

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of

attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

11.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability or Study Drug Dosing module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

11.1.8 Safety signal detection

Selected data from this study will be reviewed periodically, at least quarterly, to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study subjects, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of relevant safety data, such as AEs, results of laboratory tests and technical and physical examinations.

Any findings from this review will be brought to the attention of the DMC, that will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship with new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, or

termination of the clinical study. The precise membership, scope, and responsibilities of the DMC are described in the DMC Charter.

The Study Physician or medically qualified designee/equivalent will also conduct an ongoing reconciliation of SAEs and Pregnancy Reports between the safety and clinical databases, in collaboration with the PS representative.

11.2 Serious adverse events

11.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

11.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

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

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

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

11.2.3 Follow up of serious adverse events

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

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

11.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then

be reported if an alternative etiology is identified during investigation and monitoring of the subject. Guidance on the evaluation and management of PDILI is provided in Section 11.6.1.

11.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- Adverse events of special interest (see Section 11.3)

11.5 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. 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 11.2.2.

Table 11–1: Anticipated SAEs for the epilepsy population

MedDRA System Organ Class	MedDRA Preferred Term
Congenital, familial, and genetic disorders	Teratogenicity
General disorders and administration site disorders	Sudden unexplained death in epilepsy
Injury, poisoning, and procedural complication	Fall[a], fracture[a], injury[a]
Nervous system disorders	Cluster seizures, cognitive disorder, convulsion, incontinence[a, b], status epilepticus
Pregnancy, puerperium, and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Abnormal behavior, anxiety, confusional state, psychotic behavior, sleep disorder
Reproductive system and breast disorders	Impotence, menstrual disorder

MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=System Organ Class
[a] Event is considered to be anticipated when occurring in context of sezure.
[b] Event is not classified in MedDRA primary SOC.

11.6 Laboratory measurements

The following laboratory parameters will be measured at the scheduled time points presented in Table 5–2:

Table 11–2: Laboratory measurements

Hematology	Chemistry	Urinalysis[a]
Basophils	ALP	Total protein
Eosinophils	Calcium	Glucose

Table 11–2: Laboratory measurements

Hematology	Chemistry	Urinalysis[a]
Lymphocytes	Chloride	pH
Monocytes	Magnesium	RBC
Neutrophils	Potassium	WBC
Hematocrit	Sodium	
Hemoglobin	Glucose	
MCH	BUN or urea	
MCHC	AST	
MCV	ALT	
Platelet count	Total bilirubin	
RBC count	LDH	
WBC count	Creatinine	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell
[a] Dipstick test only

Also, a drug and alcohol screen (amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, methadone, opiates, and alcohol) will be performed at the scheduled time points presented in Table 5–2.

In addition, for females of childbearing potential, a serum pregnancy test and a urine pregnancy test (beta-human chorionic gonadotropin) will be performed at the scheduled time points presented in Table 5–2.

11.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.3), and, if applicable, also reported as an SAE (see Section 11.1.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.6.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 11.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 11–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 11.6.1.2).	Not required unless otherwise medically indicated (at discretion of the Investigator).	
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.6.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

Table 11–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 11.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.6.1.1 Consultation with the Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section11.6.1.3) and SAE report (if applicable).

11.6.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11–3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

11.6.1.2.1 IMP restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 11–3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 11.6.1.3 and Section 11.6.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the Investigator-recommended monitoring plan.

11.6.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–4 (laboratory measurements) and Table 11–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 11–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

Table 11–4: PDILI laboratory measurements

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 11–5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

11.6.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up and monitoring as described in Table 11–3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.7 Other safety measurements

11.7.1 Vital signs

Vital signs will be measured at the scheduled time points presented in Table 5–2.

Vital signs including pulse rate, systolic BP, diastolic BP, and RR will be measured in supine position, after 5 minutes of rest. Any clinically significant abnormality in the view of the Investigator will be recorded as an AE.

11.7.2 Electrocardiogram

The 12-lead ECG recordings will be measured at the scheduled time points presented in Table 5–2.

All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes. ECG will be recorded at a speed of 25mm/s and with a calibration of 1cm/mV.

The Investigator should review all ECG recordings and, if there are abnormalities that are considered clinically significant for a particular subject, then the Investigator should initiate a review by a specialist of all ECG data pertaining to that subject. The following ECG parameters will be recorded in the eCRF: heart rate, PR interval, QRS duration, QT interval, QTcB or QTcF, and Investigator's conclusion on ECG profile.

11.7.3 Echocardiogram

Echocardiograms will be recorded at the scheduled time points presented in Table 5–2. A complete echocardiography manual will be provided separately.

2-Dimensional Doppler echocardiography will be performed with:

1. Diastolic measurements (mitral forward flow E and A waves and deceleration time)
2. Tissue Doppler on medial and lateral mitral valve annulus (S, E, and A waves)
3. Standardized views for left atrial volume measurements.

Images will be recorded and stored digitally and retained if further analysis is needed. In the event that echocardiograms are not interpretable during the study, alternative assessments using either transesophageal echocardiography or cardiac magnetic resonance imaging (CMR) should be performed. Central reading of the echocardiograms may be performed by a specialized vendor.

In case of cardiac TEAEs associated with echocardiographic findings, the subject must be withdrawn from the study if the finding is clinically concerning or worsens over time, and the following should be completed:

- The subject should return for an EDV
- The subject should immediately stop the intake of UCB0942 or be down titrated as instructed at the EDV
- SFUs should be scheduled 1 week and 30 days after the subject has discontinued UCB0942

These TEAEs should be followed up at least 6 months or until they have resolved, have a stable sequelae, or the subject is lost to follow up.

11.7.4 Physical and neurological examination

Physical and neurological examinations will be performed at the scheduled time points presented in Table 5–2. The complete physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal;

hepatic; and mental status. The brief physical examination will include review of the following body systems: cardiovascular, pulmonary, abdominal (hepato-gastrointestinal), and dermatologic.

The complete neurological examination will include a selected assessment of the following: general (level of consciousness, mental status, speech, reasoning, mood), cranial nerves, reflexes, motor system (general, muscle strength, muscle tone), coordination/cerebellar function (eye movements, walking, stance, limb ataxia), and sensation. The brief neurological examination will include a selected assessment of the following: cognition, general, reflexes, muscle strength, and coordination/cerebellar function.

Findings that are considered clinically significant changes since the physical or neurological examination at the EV will be recorded as AEs.

Body weight will be measured at the scheduled time points presented in Table 5–2. Body weight will be measured with the subject in underwear or light clothing and without wearing shoes; the outcome will be rounded to the nearest 0.1kg. At the EV, the BMI will be calculated (weight [kg]/[height (m)]²) and will be reported to 1 decimal place.

11.7.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used at screening for the EP0069 study as well as to assess suicidal ideation and behavior that may occur during the current study. The C-SSRS will be completed at the scheduled time points presented in Table 5–2.

11.7.6 Psychiatric and cognitive assessments

The overall psychiatric condition of the subjects will be assessed using the BPRS questionnaire. The BPRS will be completed at the scheduled time points presented in Table 5–2. The BPRS is a questionnaire completed by the Investigator or a delegate and consists of 18 questions which capture the psychiatric condition of the subject.

The MMSE is a sensitive, valid, and reliable 30-point questionnaire completed by the Investigator. The MMSE is used extensively in clinical and research settings to measure cognitive impairment. The MMSE will be completed at the scheduled time points presented in Table 5–2.

Further details about all questionnaires used in this study and their administration will be covered in the Study Manual.

11.7.7 Monitoring symptoms of withdrawal

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire. The CIWA-B will be completed at the scheduled time points presented in Table 5–2. The CIWA-B questionnaire is completed by the subject and contains 22 questions which are selected to distinguish withdrawal symptoms from other symptoms. Further details about this questionnaire will be covered in the Study Manual.

11.7.8 Narratives of benefit and benefit-risk assessment

Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form during the Screening Period and at other

scheduled time points presented in Table 5–2. The verbatim of the attained benefits or treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be recorded as narratives by the Investigator or site personnel. The Investigator will also assess and provide a brief justification that the benefit-risk ratio for the subject on long-term treatment with the IMP supports continuation in the study, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IEC, or Sponsor.

After implementation of such measure, the Investigator must notify the Clinical Project Manager (CPM) of the Sponsor within 24 hours and follow any local regulatory requirements.

12.2 Monitoring

PRA will monitor the study to meet the PRA's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with PRA and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigators/institutions will permit direct access to source data/documents for study-related monitoring, audits, IEC review, and regulatory inspection(s).

The Investigator will allow PRA to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide PRA with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as echocardiogram results, must be saved and stored as instructed by UCB (or designee).

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 Case Report form completion

This study is performed using remote data capture. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRF once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

12.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

12.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, benefit-risk balance (0 to 4) indicating the risks outweigh the benefits, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

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

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

12.6 Audit and inspection

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

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

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

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

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

13.1 Definition of analysis sets

The Enrolled Set will consist of all enrolled subjects who have signed the Informed Consent form.

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

The Full Analysis Set (FAS) will consist of all enrolled subjects who took at least 1 dose of study medication and completed at least 1 seizure diary during the Evaluation Period.

The Pharmacokinetic Per-Protocol Set will consist of subjects in the FAS who received at least 1 dose of study medication, and did not have a major protocol deviation impacting the PK variables.

13.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Summary statistics will be presented by the overall UCB0942 group, unless otherwise indicated.

13.3 Planned safety analyses

The long-term safety of UCB0942 at individualized doses will be evaluated by means of the safety analyses. Summary tables will be presented over the study periods (Evaluation, Taper, and Safety Follow-Up) by 3-month time intervals and by categories of total duration of exposure.

All safety variables will be analyzed by descriptive methods and listed on the SS.

Treatment-emergent AEs will be summarized by study period (Evaluation, Taper, and Safety Follow-Up) by 3-month time intervals and categories of total duration of exposure, using the Medical Dictionary for Regulatory Activities (MedDRA®) primary System Organ Class (SOC) and Preferred Term in incidence tables. Separate tables will be provided for AEs leading to withdrawal from the study and SAEs overall and by the subcategories listed above.

Laboratory values, ECG data (heart rate, PR, QTc [using Bazett's and Fridericia's formula] and QRS), vital signs, and weight will be summarized by period and visit (actual values and change from baseline). Possible clinically significant treatment-emergent abnormalities for laboratory values, vital signs, and weight will be listed and summarized by period and visit. Electrocardiogram abnormalities will also be listed by period and visit.

Summary tables (and graphical outputs if needed) will be performed on the Doppler echocardiography data.

Physical and neurological examinations, psychiatric assessments (BPRS), memory or cognition from the MMSE and the withdrawal symptoms using the CIWA-B assessment will be provided as listing by period and visit (actual values and change from baseline). C-SSRS results will be displayed in a listing.

Any additional listings or tabulations will be described in the SAP.

13.4 Planned efficacy analyses

In both this study and EP0069 only POS of type IA1, IB, and IC and not non-motor IA2, IA3 or IA4 seizures will be counted for the assessment of seizure frequency and responder rate. For assessment of seizure-free rate and days, all seizure types will be considered.

13.4.1 Analysis of the primary efficacy variable

The primary efficacy variable is the 75%RR by 3-month intervals over the Evaluation Period; it will be summarized with descriptive statistics. A 75% responder is defined as a subject with a ≥75% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069. Seizure frequency will be standardized to a 28-day duration. Potential sensitivity analyses of the primary efficacy variable will be described in the SAP.

13.4.2 Analysis of the secondary efficacy variables

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

- POS frequency per 28 days by 3-month intervals over the Evaluation Period of the EP0073 study; the median will be considered as the key statistic.
- POS frequency per 28 days by seizure type by 3-month intervals over the Evaluation Period of the EP0073 study; the median will be considered as the key statistic.
- Percent reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069 by 3-month intervals over the Evaluation Period of the EP0073 study.
- 50% RR by 3-month intervals over the Evaluation Period of the EP0073 study. A 50% responder is defined as a subject with a ≥50% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069.
- Percentage of seizure-free days by 3-month intervals over the Evaluation Period.
- Seizure-free rate by 3-month intervals over the Evaluation Period.
- Changes in QOLIE-31-P scores from V3 of EP0069 through the assessment of the Evaluation Period.

13.5 Planned pharmacokinetic analyses

Plasma concentrations of UCB0942 and metabolites will be listed and summarized using descriptive statistics.

The PK samples will be taken to inform subject compliance, in addition to refinement of the UCB0942 population PK modeling. Exploratory population PK analysis will be performed

together with evaluation of longer-term (up to 1 year) exposure-response relationships to support the understanding of the clinical efficacy profile of UCB0942.

13.6 Handling of protocol deviations

After all data have been verified/entered into a database and prior to database lock, a data evaluation meeting will take place. The purpose of the data evaluation will be to examine all protocol deviations and to verify the quality of the data. The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (eg, withdrawals, dropouts, and protocol deviations).

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Study Master File. After the data review, resolution of all issues, and documentation of all decisions, the database will be locked.

13.7 Handling of dropouts or missing data

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

13.8 Planned interim analysis and data monitoring

A DMC will systematically monitor and report (at least quarterly up to the time point when the last patient entering EP0073 reaches 1 year in the study, and less frequent thereafter) on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC approximately 3 months after first dosing in EP0073. Blinded data until database lock from EP0069 and data from the OLE EP0073 studies will be reviewed in order for the DMC to provide an ongoing risk-benefit evaluation with particular reference to the occurrence of psychiatric and cardiological/cardiovascular AEs, seizure control, and any new identified safety signals. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist, none of whom will be involved with the conduct of the study, either by management or participation. In addition, there will be an independent reporting team, consisting of an independent statistician and independent statistical programmers, who will be completely independent from the blinded reporting team. The blinded reporting team will be responsible for all operational aspects of the study, including routine monitoring and cleaning of the data, programming, and quality control of all analyses defined in the interim EP0073 SAP on blinded data of EP0069 and unblinded data of EP0073 (open-label study). If required for monitoring of safety and benefit-risk of EP0073 patients, unblinded data from EP0069 study can be reviewed by the external members of the DMC at closed sessions and provided by an independent statistician. The DMC will make recommendations to the company, which may include changes to study procedures, or termination of the clinical study.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be

followed to maximize subject safety and ensure that the benefit-risk balance justifies participation in the study.

The narratives of benefit attained with UCB0942 treatment and the Investigator's justification for the concluded benefit-risk balance will be among the data reviewed by the DMC.

13.9 Determination of sample size

For this OLE study, no sample size calculation is needed. The sample size will depend upon recruitment into and completion of the previous study. It is estimated that about 40 subjects from EP0069 will enter this EP0073 study.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

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

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

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF 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.

14.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject and/or caregiver will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

14.3 Independent Ethics Committees

The study will be conducted under the auspices of an IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

UCB (or its representative) will ensure that an appropriately constituted IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, UCB (or its representative) will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IEC for its review and approval.

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

UCB (or its representative) will promptly report to the IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IEC as allowed.

As part of the IEC requirements for continuing review of approved studies, UCB (or its representative) will be responsible for submitting periodic progress reports to the IEC (based on IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. UCB (or its representative) should provide a final report to the IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide UCB (or its representative) with evidence of such IEC notification.

14.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

14.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

16 REFERENCES

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17 APPENDICES

17.1 Protocol Amendment 1

Rationale for the amendment

- Addition of a UCB0942 100mg (50mg bid) maintenance dose to allow Investigators the ability to explore the range of doses from 100mg to 800mg per day using bid dosing.
- Addition of a UCB0942 25mg tablet, which was not previously available.
- Addition of PK blood samples for measurement of plasma concentration of UCB0942 and metabolites at V3, V4, V5, V6, V7, V8, and V9. These samples will be taken to monitor subject compliance, amongst others. Exploratory population PK analysis will be performed together with evaluation of longer-term (up to 1 year) exposure-response relationships to support the understanding of the clinical efficacy profile of UCB0942.
- Change of V21 from M60 to M58. The study duration has been reduced to ensure adequate insurance coverage in case of unplanned extension of study participation of single subjects for safety reasons.
- Added that there will be no tapering from the EP0069 dose before the first dose is administered in EP0073.
- Changed text to clarify that narratives of benefit and benefit-risk assessment can be captured during the Screening Period, thus from V1 to V2.
- Change of the withdrawal criterion on suicidal ideation.
- Change of Clinical Trial Biostatistician.
- Addition of Enrolled Set.
- Minor textual changes or additions, and correction of typos.

Modifications and changes

Specific changes

Change #1

Section Study Contact Information, Clinical Project Manager

[redacted]

Has been changed to:

Dr. [redacted]

Change #2

Section Study Contact Information, Clinical Trial Biostatistician

Name: [redacted]

Address: UCB Biopharma SPRL

Chemin du Foriest

B-1420 Braine-l'Alleud

BELGIUM

Phone: [redacted]

Fax: [redacted]

Has been changed to:

Name: [redacted]

Address: UCB Biosciences Inc.

P.O. Box 110167

Research Triangle Park, NC 27709

USA

Phone: [redacted]

Fax: [redacted]

Change #3

Section List of Abbreviations

PK pharmacokinetic(s)

Has been added

Change #4

Section 1 Summary, first bullet of first bullet list

The Investigator will also provide a statement and a brief justification of positive benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942 at V1.

Has been changed to:

During the Screening Period, the Investigator will also provide a statement and a brief justification of positive benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942.

Change #5

Section 1 Summary, second bullet of first bullet list

An Evaluation Period of up to 5 years, which will start with V2, the Entry Visit (EV), which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069.

Has been changed to:

An Evaluation Period of up to approximately 5 years, which will start with V2, the Entry Visit (EV), which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069.

Change #6

Section 1 Summary, first paragraph after first bullet list

They will continue this dose in the current study; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject.

Has been changed to:

They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject.

Change #7

Section 1 Summary, first paragraph after first bullet list

Daily UCB0942 doses during this study may be 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart, except for the 100mg daily dose which is administered as a 100mg tablet once daily during the Taper Period.

Has been changed to:

Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #8

Section 1 Summary, sixth paragraph after first bullet list

The primary objective of this study is to evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 200mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy.

Has been changed to:

The primary objective of this study is to evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 100mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy.

Change #9

Section 1 Summary, sixth paragraph after first bullet list

The exploratory objective is to evaluate the plasma concentrations of UCB0942 and metabolites.

Has been added

Change #10

Section 1 Summary, last paragraph

Secondary efficacy variables are described in Section 4.2.2.

Has been changed to:

Secondary efficacy variables are described in Section 4.2.2 and the exploratory pharmacokinetic (PK) variable is described in Section 4.3.

Change #11

Section 2.3 Risks and mitigation strategy, first paragraph

In addition there are 7 important potential risks; some are specific to UCB0942 and were identified from the nonclinical and clinical databases (potential for: dependence, cardiac arrhythmia, hepatotoxicity and decreased growth) while the others are class effects (potential for: abuse, suicidality, worsening seizures).

Has been changed to:

In addition there are 7 important potential risks; some are specific to UCB0942 and were identified from the nonclinical and clinical databases (potential for: withdrawal/dependence, cardiac arrhythmia, hepatotoxicity and decreased growth) while the others are class effects (potential for: abuse, suicidality, worsening seizures).

Change #12

Section 2.3.1 Cardiac adverse events, first paragraph

A cardiologist concluded that the potential cardiac hazard of UCB0942 in humans is likely minimal; however, it is possible that epicardial or valvular changes will occur in humans with prolonged exposure (beyond 3 months).

Therefore, in this study, subjects will have an echocardiogram at Visit 1 and every 3 months for the first year and second year of treatment, and every 6 months in subsequent years to ensure early detection of any valvular or pericardial changes that may occur.

Has been changed to:

A cardiologist concluded that the potential cardiac hazard of UCB0942 in humans is likely minimal; however, it is possible that epicardial or valvular structural changes will occur in humans with prolonged exposure (beyond 3 months).

Therefore, in this study, subjects will have an echocardiogram at Visit 2 and every 3 months for the first year and second year of treatment, and every 6 months in subsequent years to ensure early detection of any valvular or pericardial changes that may occur.

Change #13

Section 3.1 Primary objective

To evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 200mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy.

Has been changed to:

To evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 100mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy.

Change #14

Section 3.3 Exploratory objective has been added, with the objective as follows:

To evaluate the plasma concentrations of UCB0942 and metabolites.

Change #15

Section 4.3 Exploratory pharmacokinetic variable has been added, with the variable as follows:

Plasma concentrations of UCB0942 and metabolites during the first 13 months of treatment in EP0073.

Change #16

Section 5.1 Study description, first bullet of first bullet list

The Investigator will also provide a statement and a brief justification of positive benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942 at V1.

Has been changed to:

During the Screening Period, the Investigator will also provide a statement and a brief justification of positive benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942.

Change #17

Section 5.1 Study description, second bullet of first bullet list

An Evaluation Period of up to 5 years, which will start with V2, the EV, which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069.

Has been changed to:

An Evaluation Period of up to approximately 5 years, which will start with V2, the EV, which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069.

Change #18

Section 5.1 Study description, first paragraph after first bullet list

They will continue this dose in the current study; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject.

Has been changed to:

They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject.

Change #19

Section 5.1 Study description, first paragraph after first bullet list

Daily UCB0942 doses during this study may be 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart, except for the 100mg daily dose which is administered as a 100mg tablet once daily during the Taper Period.

Has been changed to:

Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #20

Section 5.2 Visit schedule

In the study visit schedule (Table 5–1), M60 has been replaced by M58 and LEVP has been corrected to LEPV.

Change #21

Section 5.3 Schedule of study assessments

In the schedule of study assessments (Table 5–2), M60 has been replaced by M58.

Change #22

Section 5.3 Schedule of study assessments

In the schedule of study assessments (Table 5–2), the X for narratives of benefit and benefit-risk assessment has been moved from V1 to V2. Also the following footnote has been added:

[i] Narratives of benefit and benefit-risk assessment can be completed any time during the Screening Period after obtaining informed consent and before eligibility check at V2.

Change #23

Section 5.3 Schedule of study assessments

In the schedule of study assessments PK blood sampling has been added, including a footnote:

[k] Obtain blood samples for measurement of plasma concentration of UCB0942 and metabolites at V3, V4, V5, V6, V7, V8 and V9.

Change #24

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

Daily UCB0942 doses during this study may be 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering.

Has been changed to:

Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration.

Change #25

Section 6.3 Withdrawal criteria, criterion #4

4. Subject cannot tolerate the minimum UCB0942 dose of 100mg bid (200mg/day).

Has been changed to:

4. Subject cannot tolerate the minimum UCB0942 dose of 50mg bid (100mg/day).

Change #26

Section 6.3 Withdrawal criteria, criterion #12

12. 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.

Has been changed to:

12. Subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk of continuing the subject in the study/on study medication. Subject has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Change #27

Section 7.1 Description of investigational medicinal product(s)

The UCB0942 25mg tablet has been added to the table.

In addition, the note below the table has been changed as described below.

Note: UCB0942 tablets will be provided in bottles, containing either 80 or 200 tablets for both 100mg and 200mg dosage. Appropriate bottle size will be dispensed through the IRT system as per visit schedule and visit interval.

Has been changed to:

Note: UCB0942 tablets will be provided in bottles, containing 135 tablets for the 25mg dosage and either 80 or 200 tablets for both the 100mg and 200mg dosage. Appropriate bottle size will be dispensed through the IRT system as per visit schedule and visit interval.

Change #28

Section 7.2 Treatments to be administered, first paragraph

They will continue this dose in the current study; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject.

Has been changed to:

They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject.

Change #29

Section 7.2 Treatments to be administered, first paragraph

Daily UCB0942 doses during this study may be 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart, except for the 100mg daily dose which is administered as a 100mg tablet once daily during the Taper Period.

Has been changed to:

Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #30

Section 7.2 Treatments to be administered

In the three-week taper schedule for UCB0942 (**Error! Reference source not found.**), the 100mg maintenance dose has been added and the following footnote has been deleted:

[b] 100mg daily dose administered as a 100mg tablet once daily.

Change #31

Section 7.2 Treatments to be administered, first paragraph below Table 7–2

During the Taper Period, the dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart, except for the 100mg daily dose which is

administered as a 100mg tablet once daily during the Taper Period. Only 100mg tablets are allowed to be used during the Taper Period.

Has been changed to:

During the Taper Period, the dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart.

Change #32

Section 7.3 Packaging

UCB0942 tablets will be provided in bottles, containing either 80 or 200 tablets for both 100mg and 200mg dosage. Appropriate bottle size will be dispensed through the IRT system as per visit schedule and visit interval.

Has been changed to:

UCB0942 tablets will be provided in bottles, containing 135 tablets for the 25mg dosage and either 80 or 200 tablets for both the 100mg and 200mg dosage. Appropriate bottle size will be dispensed through the IRT system as per visit schedule and visit interval.

Change #33

Section 8.2.1 Entry Visit

Narratives of benefit and benefit-risk assessment (if not performed at V1)

Has been added

Change #34

Section 8.2.3 Minimal Evaluation Visit

Blood sample for measurement of plasma concentration of UCB0942 and metabolites (only at V3, V4, V6, and V8)

Has been added

Change #35

Section 8.2.4 Full Evaluation Visit

Blood sample for measurement of plasma concentration of UCB0942 and metabolites (only at V5 and V7)

Has been added

Change #36

Section 8.2.5 Yearly Evaluation Visit and Early Discontinuation Visit

The YEVs are planned in M13 (V9), M25 (V13), M37 (V17), M49 (V19), and M60 (V21; also LEPV).

Has been changed to:

The YEVs are planned in M13 (V9), M25 (V13), M37 (V17), M49 (V19), and M58 (V21; also LEPV).

Change #37

Section 8.2.5 Yearly Evaluation Visit and Early Discontinuation Visit

Blood sample for measurement of plasma concentration of UCB0942 and metabolites (only at V9)

Has been added

Change #38

Section 10.0 Assessment of Pharmacokinetics has been added, with the text as follows:

10.1 Sampling procedures

Blood samples for PK will be obtained at the scheduled time points presented in Table 5–2.

Exact sampling times will be recorded in the eCRF.

Detailed information on the collection, storage, preparation, and shipping of samples will be presented in a Laboratory Manual.

10.2 Bioanalytical methods

Plasma concentrations of UCB0942 and metabolites [redacted] and [redacted] will be determined using validated bioanalytical methods.

Change #39

Section 11.7.3 Echocardiogram, first paragraph after numbered list

Central reading of the echocardiograms may be performed by a specialized vendor.

Has been added

Change #40

Section 11.7.6 Psychiatric and cognitive assessments, first paragraph

The BPRS is a questionnaire completed by the Investigator or a delegate and consists of 16 questions which capture the psychiatric condition of the subject.

Has been changed to:

The BPRS is a questionnaire completed by the Investigator or a delegate and consists of 18 questions which capture the psychiatric condition of the subject.

Change #41

Section 11.7.6 Psychiatric and cognitive assessments, third paragraph

Further details about all questionnaire used in this study will be covered in the Study Manual.

Has been changed to:

Further details about all questionnaires used in this study and their administration will be covered in the Study Manual.

Change #42

Section 11.7.8 Narratives of benefit and benefit-risk assessment

Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at V1 and other scheduled time points presented in Table 5–2.

Has been changed to:

Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form during the Screening Period and at other scheduled time points presented in Table 5–2.

Change #43

Section 12.4 Termination of study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

Has been changed to:

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, negative benefit-risk balance, or unsatisfactory enrollment with respect to quality or quantity.

Change #44

Section 13.1 Definition of analysis sets

The Enrolled Set will consist of all enrolled subjects who have signed the Informed Consent form.

Has been added

Change #45

Section 13.2 General statistical considerations

Descriptive statistics, such as the mean, standard deviation, median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Summary statistics will be presented by the overall UCB0942 group, unless otherwise indicated.

Has been changed to:

Descriptive statistics, such as the mean, standard deviation, median, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, will be provided. Key supporting data will be provided in data listings. Summary statistics will be presented by the overall UCB0942 group, unless otherwise indicated.

Change #46

Section 13.4.1 Termination of study

The primary efficacy variable is the 75%RR by 3-month intervals over the Evaluation Period; it will be summarized with descriptive statistics. A 75% responder is defined as a subject with a ≥75% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069. Seizure frequency will be standardized to a 28-day duration.

Has been changed to:

The primary efficacy variable is the 75%RR by 3-month intervals over the Evaluation Period; it will be summarized with descriptive statistics. A 75% responder is defined as a subject with a ≥75% reduction in POS frequency relative to the 2-week Prospective Outpatient Baseline Period defined in EP0069. Seizure frequency will be standardized to a 28-day duration. Potential sensitivity analyses of the primary efficacy variable will be described in the SAP.

Change #47

Section 13.5 Planned pharmacokinetic analyses has been added, with the text as follows:

Plasma concentrations of UCB0942 and metabolites will be listed and summarized using descriptive statistics.

The PK samples will be taken to inform subject compliance, in addition to refinement of the UCB0942 population PK modeling. Exploratory population PK analysis will be performed together with evaluation of longer-term (up to 1 year) exposure-response relationships to support the understanding of the clinical efficacy profile of UCB0942.

17.2 Protocol Amendment 2

Rationale for the amendment

- To update the protocol information pertaining to potential drug-induced liver injury (exclusion criteria, withdrawal criteria, adverse events of special interest, and assessment of safety) based on new standard language which is being applied across all protocols at UCB. Note that these additions do not reflect a change in the known safety of the compound.
- Changed text to clarify when the DMC is to review the benefit-risk balance of subjects entering the study.
- Changed text regarding psychiatric events to align with the updated Investigator's Brochure.
- The PRA Medical Monitor has been added to the UCB Study Physician as contact point for the sites where appropriate.
- Added text to allow for exceptions in the daily UCB0942 doses after consultation with the UCB Study Physician or PRA Medical Monitor.
- Increase in estimate of approximately number of subjects from EP0069 who will be included in EP0073 to approximately 40.
- Removed text on additional contraceptive measures for the partners of male subjects, based on nonclinical data.
- Added text to have information regarding surgical evaluation, working status, caregiver support, and supervision collected at the Entry Visit.
- Changed text to clarify prohibited medications.
- Changed text to clarify withdrawal actions for subjects developing psychiatric/mood/behavioral signs or disturbances.
- Change of Clinical Project Manager.
- Additional IMP manufacturer included.
- Minor textual changes or additions, and correction of typos.

Modifications and changes

Specific changes

Change #1

Section Study Contact Information, Clinical Project Manager

Name:	Dr. [redacted]
Address:	UCB Biosciences GmbH Alfred-Nobel-Straße 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	UCB Biosciences GmbH Alfred-Nobel-Straße 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section List of Abbreviations

The following abbreviation has been deleted:

LFT liver function test

The following abbreviations have been added:

ALP alkaline phosphatase

PDILI potential drug-induced liver injury

Change #3

Section 1 Summary, fourth paragraph and first paragraph after second bullet list

A Data Monitoring Committee (DMC) will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the investigational medicinal product (IMP). The benefit-risk balance of

every subject entering the study will be reviewed by the DMC within 3 months after inclusion. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study.

Subjects being enrolled in the current study from EP0069 will be on UCB0942 400mg twice daily (bid) or a tapered UCB0942 dose of 200mg bid at the EV. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Has been changed to (changes bolded):

A Data Monitoring Committee (DMC) will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the investigational medicinal product (IMP). The benefit-risk balance of every subject entering the study will be reviewed by the DMC within **approximately** 3 months after **first dosing in EP0073**. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study.

Subjects being enrolled in the current study from EP0069 will **enter EP0073 on the dose they received in EP0069**. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg **twice daily [**bid**]**), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. **Exceptions may be allowed after consultation with the UCB Study Physician or PRA Medical Monitor.** The dose of UCB0942 must always be administered as bid morning and evening doses,

approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #4

Section 2.3.2 Psychiatric adverse events

In the multiple ascending dose study, 1 healthy volunteer had a "delirious syndrome" with prominent psychotic symptoms, and in a subsequent Phase 1 study, 1 healthy volunteer had "mania-like symptoms." Both of these AEs were classified as SAEs because the subjects required hospitalization. In both cases, the subjects fully recovered. After these psychiatric SAEs occurred, close psychiatric monitoring was implemented. Therefore, when 2 other healthy volunteers began to develop "hypomania" and "aggressive state," respectively, the symptoms were discovered early, and discontinuation of UCB0942 possibly prevented the development of these symptoms into more severe psychiatric symptoms. Based on this, it appears that close psychiatric monitoring during the first 2 weeks of dosing, and tapering and discontinuation of the drug in subjects who start to develop psychiatric AEs, will reduce the risk that subjects develop more severe psychiatric AEs or psychiatric SAEs.

In EP0069, daily psychiatric monitoring will be performed in all subjects for the first 2 weeks after dosing starts, and weekly thereafter. In the current OLE study, subjects will have a psychiatric (BPRS) and cognitive (MMSE) assessment at study visits every 3 months for years 1, 2 and 3 and every 6 months for years 4 and 5. The CIWA-B will be performed at the LEPV (last visit prior to the Taper Period)/EDV, at the visit at the end of the Taper Period) and at SFU1 and SFU2 (1 week and 30 days after administration of the final dose of UCB0942, respectively). In addition, to further reduce the risk that participating subjects develop psychiatric AEs, subjects with a history of psychosis, schizophrenia, bipolar disorder, or severe unipolar depression will be excluded from this study. Lastly, based on the fact that titration has been shown to reduce the incidence of other AEs and increase the general tolerability of UCB0942, titration may also reduce the risk of psychiatric AEs.

Has been changed to (changes bolded):

In the course of UCB0942 development, 3 psychiatric SAEs (delirious syndrome, mania-like symptoms, and acute psychosis) have been reported in 2 healthy volunteers and 1 patient with resistant epilepsy, respectively. The events were transient, acute, and required admission to psychiatric care and antipsychotics. The events in healthy subjects occurred early after initiation of UCB0942, which was done without titration. In 1 of the subjects symptoms worsened upon abrupt drug discontinuation. The psychotic effect in the epilepsy subject emerged after dramatic improvement in seizures control and electroencephalographic activity a few weeks after start of UCB0942, suggesting "forced normalization" (Loganathan et al, 2015; Clemens, 2005). Dose reduction of UCB0942 and neuroleptic treatment resulted in complete resolution of psychosis within days, as the treatment with UCB0942 continued.

In EP0069, daily psychiatric monitoring **is** performed in all subjects for the first 2 weeks after dosing starts, and weekly thereafter. In the current OLE study, subjects will have a psychiatric (BPRS) and cognitive (MMSE) assessment at study visits every 3 months for years 1, 2 and 3 and every 6 months for years 4 and 5. The CIWA-B will be performed at the LEPV (last visit prior to the Taper Period)/EDV, at the visit at the end of the Taper Period) and at SFU1 and

SFU2 (1 week and 30 days after administration of the final dose of UCB0942, respectively). In addition, to further reduce the risk that participating subjects develop psychiatric AEs, subjects with a history of psychosis, schizophrenia, bipolar disorder, or severe unipolar depression will be excluded from this study. Lastly, based on the fact that titration has been shown to reduce the incidence of other AEs and increase the general tolerability of UCB0942, titration may also reduce the risk of psychiatric AEs.

Change #5

Section 5.1 Study description, third paragraph and first paragraph after second bullet list

A DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the IMP. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within 3 months after inclusion. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study.

Subjects being enrolled in the current study from EP0069 will be on UCB0942 400mg bid or a tapered UCB0942 dose of 200mg bid at the EV. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Has been changed to (changes bolded):

A DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the IMP. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within **approximately** 3 months after **first dosing in EP0073**. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study.

Subjects being enrolled in the current study from EP0069 will **enter EP0073 on the dose they received in EP0069**. They will continue this dose in the current study and there will be no

tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. **Exceptions may be allowed after consultation with the UCB Study Physician or PRA Medical Monitor.** The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #6

Section 5.1.2 Planned number of subjects and sites

It is estimated that approximately 30 subjects who completed EP0069 will be included in multiple sites in Europe.

Has been changed to (change bolded):

It is estimated that approximately **40** subjects who completed EP0069 will be included in multiple sites in Europe.

Change #7

Section 5.3 Schedule of study assessments, Table 5-2, footnote (b)

[b] From EP0069 study. Update if necessary.

Has been changed to:

[b] Demographic and general medical/procedure history data will be obtained from EP0069 and updated if necessary. Information regarding surgical evaluation, working status, caregiver support, and supervision should be collected within 30 days after Protocol Amendment 2 is approved.

Change #8

Section 5.4 Rationale for study design and selection of dose, second and last paragraphs

Subjects being enrolled in the current study from EP0069 will be on UCB0942 400mg bid or a tapered UCB0942 dose of 200mg bid at the EV. The highest UCB0942 dose of 400mg bid used in this study has been chosen because it is the maximum tolerated dose in Phase 1 studies.

Throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the

Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration.

Has been changed to (changes bolded):

Subjects being enrolled in the current study from EP0069 will **enter EP0073 on the dose they received in EP006. In EP0073 doses can range from 50mg bid to 400mg bid.** The highest UCB0942 dose of 400mg bid used in this study has been chosen because it is the maximum tolerated dose in Phase 1 studies.

Throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration **unless agreed by the UCB Study Physician or PRA Medical Monitor.**

Change #9

Section 6.1 Inclusion criteria, Inclusion Criterion #8 (bolded text has been deleted)

Male subject confirms that, during the study period and for a period of 3 months after the final dose, when having sexual intercourse with a woman of childbearing potential, he will use a barrier contraceptive (eg, condom) **AND that the respective partner will use an additional contraceptive method**.

Has been changed to:

Male subject confirms that, during the study period and for a period of 3 months after the final dose, when having sexual intercourse with a woman of childbearing potential, he will use a barrier contraceptive (eg, condom).

Change #10

Section 6.2 Exclusion criteria

Added the following Exclusion Criterion #12:

Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome) at the EV (V2) of EP0073 (V15 of EP0069). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For enrolled subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening (ie, the value is >ULN but ≤2xULN at the EV [V2] of EP0073), repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

Change #11

Section 6.3 Withdrawal criteria, third paragraph

Investigators should contact the UCB Study Physician, whenever possible, to discuss the withdrawal of a subject in advance.

Has been changed to (change bolded):

Investigators should contact the UCB Study Physician **or PRA Medical Monitor**, whenever possible, to discuss the withdrawal of a subject in advance.

Change #12

Section 6.3 Withdrawal criteria, Withdrawal Criterion #2

In the case of liver function test (LFT) results of transaminases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) ≥3x upper limit of normal (ULN) to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST and/or ALT) ≥5x ULN, UCB0942 must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Has been deleted

Change #13

Section 6.3 Withdrawal criteria, previous Withdrawal Criterion #3 (currently #2), last 2 bullets

- ALT ≥2x ULN
- AST ≥2x ULN

Have been deleted

Change #14

Section 6.3 Withdrawal criteria, previous Withdrawal Criterion #8 (currently #7), first and last bullets

- Carbamazepine, phenytoin, phenobarbital, primidone, or other strong CYP3A4 inducers
- Non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products)

Have been changed to (changes bolded):

- Carbamazepine, phenytoin, phenobarbital, primidone, or other **AEDs that are** strong CYP3A4 inducers
- **Strong n**on-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products)

(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

Change #15

Section 6.3 Withdrawal criteria, previous Withdrawal Criterion #17 (currently #16), paragraph

Subject develops psychiatric/mood/behavioral signs or disturbances (see examples in list below) that are clinically concerning or that worsen over time. Tapering and discontinuation of UCB0942 should be performed in such subjects and they should be referred to a mental health professional.

Has been changed to (changes bolded):

For subjects develop**ing** psychiatric/mood/behavioral signs or disturbances (see examples in list below) that are clinically concerning or that worsen over time, **the study drug dose should be gradually reduced and, if symptoms persist, withdrawal from study should be recommended. Subjects** should be referred to a mental health professional, **and continuation of the study treatment should only be allowed with the approval and under close oversight of the mental health specialist, and upon confirmation of the positive benefit-risk by the Investigator**.

Change #16

Section 6.3 Withdrawal criteria

Added Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria:

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 11.6.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Change #17

Section 7.1 Description of investigational medicinal product(s), Table 7-1, Manufacturer

The following text has been added:

Catalent Micron Technologies

Crossways Boulevard

Crossways Dartford, Kent

DA2 6QY United Kingdom

Change #18

Section 7.2 Treatments to be administered, first and third paragraphs

Subjects being enrolled in the current study from EP0069 will be on UCB0942 400mg bid or a tapered UCB0942 dose of 200mg bid at the EV. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. The UCB Study Physician must be consulted prior to initiation of concomitant AED withdrawal. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction, if the concomitant medication has been approved for focal seizures by the health authority of the subject's country of residence, taking the drug to drug interactions profile of UCB0942 into account. New AEDs (with the exception of AEDs

listed in the prohibited medication section, Section 7.8.2) should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of UCB0942.

Have been changed to (changes bolded):

Subjects being enrolled in the current study from EP0069 will **continue their** dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and **titration unless agreed by the UCB Study Physician or PRA Medical Monitor.** The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. The UCB Study Physician **or PRA Medical Monitor** must be consulted prior to initiation of concomitant AED withdrawal. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction, if the concomitant medication has been approved for focal seizures by the health authority of the subject's country of residence, taking the drug to drug interactions profile of UCB0942 into account. New AEDs (with the exception of AEDs listed in the prohibited medication section, Section 7.8.2) should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of UCB0942.

Change #19

Section 7.8.1 Permitted concomitant treatments (medications and therapies), first and last bullets (bolded text has been deleted)

- All subjects will enter EP0073 using their current AED regimen. Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject. Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction. Changes in AEDs should be discussed with the UCB Study Physician on an individual and case-by-case basis.
- Other medication, not mentioned as prohibited**, that does not induce CYP3A4 and is approved by the UCB Study Physician**.

Have been changed to (change bolded):

- All subjects will enter EP0073 using their current AED regimen. Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction. Changes in AEDs should be discussed with the UCB Study Physician **or PRA Medical Monitor** on an individual and case-by-case basis.

- Other medication, not mentioned as prohibited.

Change #20

Section 7.8.2 Prohibited concomitant treatments (medications and therapies), first, second, and last bullets

- Carbamazepine, phenytoin, phenobarbital, primidone, or other strong CYP3A4 inducers
- Benzodiazepines taken >3 times per week
- Non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products)

Have been changed to (changes bolded):

- Carbamazepine, phenytoin, phenobarbital, primidone, or other **AEDs that are** strong CYP3A4 inducers
- Benzodiazepines taken >3 times per week **(ie, >3 doses within 7 days)**
- **Strong n**on-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products) **(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)**

Change #21

Section 7.9 Blinding

This is an OLE study so no blinding is required. A DMC (see Section 13.8) will review blinded data up until final database lock from EP0069 and data from the OLE EP0073 studies in order for the DMC to provide an ongoing evaluation of the safety signals and the benefit-risk balance for the study subjects.

Has been changed to (changes bolded):

This is an OLE study so no blinding is required. A DMC (see Section 13.8) will review blinded data up until final **unblinding** from EP0069 and data from the OLE EP0073 studies **to** provide an ongoing evaluation of the safety signals and the benefit-risk balance for the study subjects.

Change #22

Section 8.2.1 Entry Visit, paragraph and first 2 bullets

The EV, V2, is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. During the EV the following assessments will be performed:

- Review demographic, medical, medication, and procedural data from EP0069; update where necessary.

- Concomitant AEDs and non-AEDs; ongoing medications (AEDs and non-AEDs) at the time of subject completion of EP0069 will be obtained from the database for EP0069 and should not be recorded in the eCRF for EP0073 unless there is a change regarding the administration of the medication. In this event, the medication should be recorded in the eCRF for EP0073 with the start date corresponding to the date of change in administration.

Have been changed to (changes bolded):

The EV, V2, is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. **Data collected at V15 in EP0069 must also be recorded at V2 in the EP0073 eCRF.** During the EV the following assessments will be performed:

- Review demographic, medical, medication, and procedural data from EP0069 **and** update where necessary**; collect information regarding surgical evaluation, working status, caregiver support, and supervision within 30 days after Protocol Amendment 2 is approved**.
- Concomitant AEDs and non-AEDs; **any** ongoing **concomitant** medications **from EP0069 must also be recorded on the EP0073 eCRF. Details are provided in the eCRF Completion Guidelines.**

Change #23

Section 11.1.8 Safety signal detection, third paragraph

Any findings from this review will be brought to the attention of the DMC, that will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship with new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within 3 months after inclusion. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit risk balance, or termination of the clinical study. The precise membership, scope, and responsibilities of the DMC are described in the DMC Charter.

Has been changed to (changes bold):

Any findings from this review will be brought to the attention of the DMC, that will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship with new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within **approximately** 3 months after **first dosing in EP0073**. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study. The precise membership, scope, and responsibilities of the DMC are described in the DMC Charter.

Change #24

Section 11.3 Adverse events of special interest, second paragraph

There are no AEs of special interest to be reported for UCB0942.

Has been changed to:

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

Change #25

Section 11.6 Laboratory assessments

Added Section 11.6.1 Evaluation of PDILI:

11.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.3), and, if applicable, also reported as an SAE (see Section 11.1.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.6.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also

consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 11.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 11-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 11.6.1.2).	Not required unless otherwise medically indicated (at discretion of the Investigator).	
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.6.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

Table 11-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 11.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.6.1.1 Consultation with the Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section11.6.1.3) and SAE report (if applicable).

11.6.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11–3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

11.6.1.2.1 IMP restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 11–3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 11.6.1.3 and Section 11.6.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the Investigator-recommended monitoring plan.

11.6.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–4 (laboratory measurements) and Table 11–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 11-4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

Table 11-4: PDILI laboratory measurements

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 11-5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

11.6.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up and monitoring as described in Table 11–3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

Change #26

Section 13.8 Planned interim analysis and data monitoring, first paragraph

A DMC will systematically monitor and report (at least quarterly up to the time point when the last patient entering EP0073 reaches 1 year in the study, and less frequent thereafter) on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the

ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within 3 months after inclusion. Blinded data until database lock from EP0069 and data from the OLE EP0073 studies will be reviewed in order for the DMC to provide an ongoing risk benefit evaluation with particular reference to the occurrence of psychiatric and cardiological/cardiovascular AEs, seizure control, and any new identified safety signals.

Has been changed to (changes bolded):

A DMC will systematically monitor and report (at least quarterly up to the time point when the last patient entering EP0073 reaches 1 year in the study, and less frequent thereafter) on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC **approximately** 3 months after **first dosing in EP0073**. Blinded data until database lock from EP0069 and data from the OLE EP0073 studies will be reviewed in order for the DMC to provide an ongoing risk benefit evaluation with particular reference to the occurrence of psychiatric and cardiological/cardiovascular AEs, seizure control, and any new identified safety signals.

Change #27

Section 13.9 Determination of sample size

For this OLE study, no sample size calculation is needed. The sample size will depend upon recruitment into and completion of the previous study. It is estimated that about 30 subjects (75%) from EP0069 will enter this EP0073 study.

Has been changed to (change bolded):

For this OLE study, no sample size calculation is needed. The sample size will depend upon recruitment into and completion of the previous study. It is estimated that about **40 subjects from** EP0069 will enter this EP0073 study.

Change #28 Section 16 References

The following 2 references have been added:

Clemens B. Forced normalisation precipitated by lamotrigine. Seizure. 2005; 14:485-9.

Loganathan MA, Enja M, Lippmann S. FORCED NORMALIZATION: Epilepsy and Psychosis Interaction. Innov Clin Neurosci. 2015; 12(5-6): 38–41.

17.3 Protocol Amendment 3

Rationale for the amendment

The primary purpose of this substantial amendment is to change the frequency for the echocardiogram assessments after the YEAR 2. Of note, no subjects have reached this milestone at the time of this protocol amendment, and therefore no impact on the safety analysis is expected. The changes made to a footnote in the Schedule of Events and text in the Study Procedures by Visit section are consistent with the original intention as stated in Section 2.3.1 in the original protocol and subsequent amendments: "subjects will have an echocardiogram at Visit 2 and every 3 months for the first year and second year of treatment, and every 6 months in subsequent years to ensure early detection of any valvular or pericardial changes that may occur." In addition, following the annual revision of the Investigator's Brochure 2017 for padsevonil, the following prohibited concomitant medications have been added in this protocol: strong CYP2C19 inhibitors, strong CYP2C19 inducers, and CYP2C19 sensitive substrates. It is to be specified that the because recruitment has been completed for EP0073, subjects who were already taking these medications prior to Amendment 3, may continue to do so, but close monitoring should be implemented.

The other main changes in this amendment are as follows:

- Clarified that a subject with a benefit-risk ratio of 0 to 4 (on a scale from 0 to 10) must be withdrawn from the study.
- Removed the UCB Study Physician as one of the contact points for the sites (PRA Medical Monitor remains in place).
- Added adverse events of special interest to the list of AEs requiring immediate reporting.
- Updated text to allow alternate assessments if echocardiograms are not usable during the study.
- Deleted text that states subjects with a positive benefit-risk ratio (6 to 10) are allowed to continue in the study, since subjects with a neutral benefit-risk ratio (5) are also allowed to continue.
- Defined the Pharmacokinetic Per-Protocol Set that will be used for the PK analysis. This is to fulfill an omission in the previous version of the protocols. No change in the SAP has occurred.
- Simplified the sections related to the IMP.

Modifications and changes

Specific changes

Change #1

List of Abbreviations, the following abbreviations have been added:

CMR cardiac magnetic resonance

DDI drug-drug interaction(s)

FAS Full Analysis Set

Change #2

STUDY CONTACT INFORMATION

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB Biosciences Inc. P.O. Box 110167 Research Triangle Park, NC 27709 USA
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB Pharma Ltd. 280 Bath Road Berkshire SL 13WE Slough UK
Phone:	[redacted]

Change #3

Section 1 Summary, fourth paragraph, first bullet, second bullet (first paragraph only), and first paragraph after the second bullet list

A Data Monitoring Committee (DMC) will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the investigational medicinal product (IMP). The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limited inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study.

The study will consist of:

- A 2-week Screening Period from Visit 13 (V13) to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study. At this visit, informed consent will be

signed and inclusion and exclusion criteria (from the current OLE study) will be checked. The verbatim of the attained benefits of treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be captured as narratives and filled in by the Investigator or site personnel. During the Screening Period, the Investigator will also provide a statement and a brief justification of positive benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942. These narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be maintained as source documents and will be reviewed by the DMC.

- An Evaluation Period of up to approximately 5 years, which will start with V2, the Entry Visit (EV), which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Eligible subjects will enter EP0073 before the planned dose tapering in EP0069. Subjects will be issued and return seizure diaries during each visit. Subjects must be educated to record all types of seizures that occur, any illness or injury, and all study medication intake in their seizure diary and be educated to complete their diary entries after each seizure or at least once a day. Throughout the study, the Investigator also will be requested to periodically re-assess and re-confirm that the benefit-risk ratio for the subject of the long-term treatment with the IMP, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options, remains positive. Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at the scheduled time points presented in Table 5-2.

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg twice daily [bid]), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. Exceptions may be allowed after consultation with the UCB Study Physician or PRA Medical Monitor. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Has been changed to (change bolded):

A Data Monitoring Committee (DMC) will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the investigational medicinal product (IMP). The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make

recommendations to the company about continuation of the study, which may include changes to **study procedures, or termination** of the clinical study.

The study will consist of:

- A 2-week Screening Period from Visit 13 (V13) to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study. At this visit, informed consent will be signed and inclusion and exclusion criteria (from the current OLE study) will be checked. The verbatim of the attained benefits of treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be captured as narratives and filled in by the Investigator or site personnel. During the Screening Period, the Investigator will also provide a statement and a brief justification of **the benefit-risk** balance for each subject's participation in EP0073 and long-term treatment with UCB0942. These narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be maintained as source documents and will be reviewed by the DMC.
- An Evaluation Period of up to approximately 5 years, which will start with V2, the Entry Visit (EV), which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Eligible subjects will enter EP0073 before the planned dose tapering in EP0069. Subjects will be issued and return seizure diaries during each visit. Subjects must be educated to record all types of seizures that occur, any illness or injury, and all study medication intake in their seizure diary and be educated to complete their diary entries after each seizure or at least once a day. Throughout the study, the Investigator also will be requested to periodically re-assess and re-confirm that the benefit-risk ratio for the subject **on** long-term treatment with the IMP, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options, **justifies continuation in the study.** Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at the scheduled time points presented in Table 5-2.

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg twice daily [bid]), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. Exceptions may be allowed after consultation with the **PRA Medical Monitor**. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #4

Section 2.3 Risks and mitigation strategy

The two important identified risks based on the human pharmacology studies to date include drug-drug interactions with potent cytochrome P450 (CYP) 3A4 enzyme inducers and the risk of developing psychiatric symptoms. The potential risk for epicardial/valvular inflammation was identified from the cardiac histopathology findings in the 39-week dog toxicology study. In addition there are 7 important potential risks; some are specific to UCB0942 considering nonclinical and clinical data (potential for: withdrawal/dependence, cardiac arrhythmia, hepatotoxicity and decreased growth) while the others are class effects (potential for: abuse, suicidality, worsening seizures).

All identified and potential risks, with the exception of decreased growth (applicable only to pediatric studies) will be appropriately mitigated in the proposed clinical study. Clinical data from this study, from EP0069, and any other relevant data becoming available (such as preclinical data) will be reviewed by a DMC that will include internal UCB and external medical experts (see Section 11.1.8), to detect and characterize as early as possible any concern(s) related to UCB0942 so that Investigators, clinical study subjects, regulatory authorities, and Institutional Review Boards/Independent Ethics Committees (IECs) are informed timely and appropriately of any significant information that affects the benefit-risk balance of the UCB0942 and participation in the study. The specific mitigation measures for cardiac AEs, psychiatric events and drug-drug interactions are discussed further below.

Has been changed to:

The important identified risks based on clinical data include the development of acute psychiatric effects and drug-drug interactions (DDIs) with strong cytochrome P450 (CYP) 3A4 enzyme inducers leading to decreased exposure levels of UCB0942. There are also some important potential risks that are UCB0942-specific based on clinical data, including impairment of cognitive and psychomotor performance, DDI between UCB0942 with CYP2C19 substrates leading to increased levels of these substrates, and decrease in blood pressure. In addition, there are several potential risks for UCB0942 that are class effects or known for other products, including suicidality, worsening of seizures, substance abuse and dependence, tolerance to the anticonvulsant effects of the drug, and decreased bone mineral density. Finally, there are a number of potential risks that are UCB0942-specific based on nonclinical data, including epicardial and valvular inflammation and epicardial fibroplasia with administration longer than 13 weeks, QT prolongation, hepatoxicity, DDI with strong CYP3A4 inhibitors leading to increased exposure levels of UCB0942, DDI with strong CYP2C19 inhibitors or inducers leading to increased or decreased exposure levels of UCB0942, and growth retardation.

All identified and potential risks, with the exception of decreased growth (applicable only to pediatric studies) will be appropriately mitigated in the proposed clinical study. Clinical data from the completed study EP0069 have been reviewed by a DMC that included internal UCB and external medical experts. Data from this study and any other relevant data that become available (such as preclinical data) will be reviewed by the DMC in order to detect and characterize as early as possible any concern(s) related to UCB0942 (see Section 11.1.8). Investigators, clinical study subjects, regulatory authorities, and Institutional Review Boards/Independent Ethics Committees (IECs) will be informed in a timely manner of any

significant information that affects the benefit-risk balance of the UCB0942 and participation in the study. The specific mitigation measures for cardiac AEs, psychiatric events and drug-drug interactions are discussed further below, and additional details about risks and mitigation strategy are provided in Section 6 of the Investigator's Brochure.

Change #5

Section 2.3.2 Psychiatric adverse events, Paragraph 2 (deletions bolded)

In EP0069, daily psychiatric monitoring is performed in all subjects for the first 2 weeks after dosing starts, and weekly thereafter. In the current **OLE** study, subjects will have a psychiatric (BPRS) and cognitive (MMSE) assessment at study visits every 3 months for years 1, 2 and 3, and every 6 months for years 4 and 5. The CIWA-B will be performed at the LEPV (last visit prior to the Taper Period)/EDV, at the visit at the end of the Taper Period) and at SFU1 and SFU2 (1 week and 30 days after administration of the final dose of UCB0942, respectively). In addition, to further reduce the risk that participating subjects develop psychiatric AEs, subjects with a history of psychosis, schizophrenia, bipolar disorder, or severe unipolar depression will be excluded from this study. Lastly, based on the fact that titration has been shown to reduce the incidence of other AEs and increase the general tolerability of UCB0942, titration may also reduce the risk of psychiatric AEs.

Has been changed to:

In the current study, subjects will have a psychiatric (BPRS) and cognitive (MMSE) assessment at study visits every 3 months for years 1, 2 and 3, and every 6 months for years 4 and 5. The CIWA-B will be performed at the LEPV (last visit prior to the Taper Period)/EDV, at the visit at the end of the Taper Period) and at SFU1 and SFU2 (1 week and 30 days after administration of the final dose of UCB0942, respectively). In addition, to further reduce the risk that participating subjects develop psychiatric AEs, subjects with a history of psychosis, schizophrenia, bipolar disorder, or severe unipolar depression will be excluded from this study. Lastly, based on the fact that titration has been shown to reduce the incidence of other AEs and increase the general tolerability of UCB0942, titration may also reduce the risk of psychiatric AEs.

Change #6

Section 2.3.3 Drug-drug interactions

A drug-drug interaction study in subjects with epilepsy showed that carbamazepine – a strong CYP3A4 inducer – reduced UCB0942 plasma exposure by >85%. Therefore, subjects on carbamazepine or other strong CYP3A4 inducers (eg, phenytoin, phenobarbital, or primidone) will not be enrolled in this study because the plasma exposure may be too low to produce any therapeutic benefit.

Has been changed to (change bolded)

A drug-drug interaction study in subjects with epilepsy showed that carbamazepine – a strong CYP3A4 inducer – reduced UCB0942 plasma exposure by >85%. Therefore, subjects on carbamazepine or other strong CYP3A4 inducers (eg, phenytoin, phenobarbital, or primidone) will not be enrolled in this study because the plasma exposure may be too low to produce any therapeutic benefit.

Preclinical data indicate the potential involvement of CYP2C19 in the metabolism of UCB0942.While the contribution of CYP2C19 is still unclear regarding the degree to which it contributes to the metabolism of UCB0942 or its metabolites, both strong inhibitors and inducers of CYP2C19 will also be prohibited. Additionally, in studies with human study participants, drug-drug interaction of UCB0942 (perpetrator) with CYP2C19 substrates (victims) was observed leading to increased levels of CYP2C19 substrates. Therefore, concomitant use of sensitive CYP2C19 substrates will be prohibited in EP0073. If subjects are already taking strong inducers or inhibitors or sensitive substrates of CYP2C19 prior to Amendment 3, they may continue to do so, but close monitoring should be implemented.

Change #7

Section 5.1 Study description, third paragraph, first bullet, second bullet (first paragraph only), and first paragraph after the second bullet list

A DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the IMP. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study.

The study will consist of:

- A 2-week Screening Period from V13 to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study. At this visit, informed consent will be signed and inclusion and exclusion criteria (from the current OLE study) will be checked. The verbatim of the attained benefits of treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be captured as narratives and filled in by the Investigator or site personnel. During the Screening Period, the Investigator will also provide a statement and a brief justification of positive benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942. These narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be maintained as source documents and will be reviewed by the DMC.
- An Evaluation Period of up to approximately 5 years, which will start with V2, the EV, which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Eligible subjects will enter EP0073 before the planned dose tapering in EP0069. Subjects will be issued and return seizure diaries during each visit. Subjects must be educated to record all types of seizures that occur, any illness or injury, and all study medication intake in their seizure diary and be educated to complete their diary entries after each seizure or at least once a day. Throughout the study, the Investigator also will be requested to periodically re-assess and re-confirm that the benefit-risk ratio for the subject of the long-term treatment with the IMP, considering the knowledge of the IMP's efficacy and safety profile and

alternative treatment options, remains positive. Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at the scheduled time points presented in Table 5-2.

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. Exceptions may be allowed after consultation with the UCB Study Physician or PRA Medical Monitor. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Has been changed to (change bolded):

A DMC will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the IMP. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to **study procedures, or termination** of the clinical study.

The study will consist of:

- A 2-week Screening Period from V13 to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study. At this visit, informed consent will be signed and inclusion and exclusion criteria (from the current OLE study) will be checked. The verbatim of the attained benefits of treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be captured as narratives and filled in by the Investigator or site personnel. During the Screening Period, the Investigator will also provide a statement and a brief justification of **the** benefit-risk balance for each subject's participation in EP0073 and long-term treatment with UCB0942. These narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be maintained as source documents and will be reviewed by the DMC.
- An Evaluation Period of up to approximately 5 years, which will start with V2, the EV, which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069. Eligible subjects will enter EP0073 before the planned dose tapering in EP0069. Subjects will be issued and return seizure diaries during each visit. Subjects must be educated

to record all types of seizures that occur, any illness or injury, and all study medication intake in their seizure diary and be educated to complete their diary entries after each seizure or at least once a day. Throughout the study, the Investigator also will be requested to periodically re-assess and re-confirm that the benefit-risk ratio for the subject **on** long-term treatment with the IMP, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options, **justifies continuation in the study**. Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form at the scheduled time points presented in Table 5-2.

Subjects being enrolled in the current study from EP0069 will enter EP0073 on the dose they received in EP0069. They will continue this dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration. Exceptions may be allowed after consultation with the **PRA Medical Monitor**. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Change #8

Section 5.3 Schedule of study assessments, Table 5-2, footnote d

[d] No echocardiogram will be done at V3.

Has been changed to (change bolded):

[d] No echocardiogram will be done at V3**, V14, and V16.**

Change #9

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

Throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration unless agreed by the UCB Study Physician or PRA Medical Monitor.

Has been changed to (change bolded):

Throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration unless agreed by the **PRA Medical Monitor**.

Change #10

Section 6.3 Withdrawal criteria, third paragraph and Withdrawal Criterion #1

Investigators should contact the UCB Study Physician or PRA Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

Subjects must be withdrawn from the study if any of the following events occur:

1. Withdrawal for safety reasons by the Investigator and/or when the benefit-risk ratio of the IMP treatment is considered negative.

Has been changed to (change bolded):

Investigators should contact the **PRA Medical Monitor**, whenever possible, to discuss the withdrawal of a subject in advance.

Subjects must be withdrawn from the study if any of the following events occur:

1. Withdrawal for safety reasons by the Investigator and/or when the benefit-risk ratio of the IMP treatment is **0 to 4 (on a scale from 0 to 10), indicating the risks outweigh the benefits**.

Change #11

Section 7.1 Description of investigational medicinal product(s)

The details of the UCB0942 IMP are displayed in Table 7-1.

Table 7-1: Description of investigational medicinal product

	UCB0942 25mg	UCB0942 100mg	UCB0942 200mg
Dosage form	White, film-coated tablet	White, film-coated tablet	White, film-coated tablet

	UCB0942 25mg	UCB0942 100mg	UCB0942 200mg
Manufacturers	Aptuit (Verona) S.r.l. Via Flemming 4 37135 Verona Italy Catalent Micron Technologies Crossways Boulevard Crossways Dartford, Kent DA2 6QY United Kingdom		
Batch/lot number	Will be assigned according to GMP		
Expiry date	Will be assigned according to GMP		

GMP=Good Manufacturing Practice; IRT=interactive response technology

Note: UCB0942 tablets will be provided in bottles, containing 135 tablets for the 25mg dosage and either 80 or 200 tablets for both the 100mg and 200mg dosage. Appropriate bottle size will be dispensed through the IRT system as per visit schedule and visit interval.
Note: 100 and 200mg tablets are the same size and appearance.

Has been changed to:

The table has been deleted and replaced with the following sentence:

The IMP is supplied as white, film-coated tablets in strengths of 25mg, 100mg, and 200mg.

Change #12

Section 7.2 Treatments to be administered, first and third paragraphs

Subjects being enrolled in the current study from EP0069 will continue their dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration unless agreed by the UCB Study Physician or PRA Medical Monitor. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. The UCB Study Physician or PRA Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction, if the concomitant medication has been approved for focal seizures by the health authority of the subject's country of residence, taking the drug-to-drug interactions profile of UCB0942 into account. New AEDs (with the exception of AEDs listed in the prohibited medication section, Section 7.8.2) should be added only when

the subject has not optimally or adequately responded to a maximum tolerated dose of UCB0942.

Has been changed to (change bolded):

Subjects being enrolled in the current study from EP0069 will continue their dose in the current study and there will be no tapering from the EP0069 dose before they receive the first dose in EP0073; however, throughout the Evaluation Period, the Investigator will be allowed to increase or decrease the dose of UCB0942 to optimize tolerability and seizure control for each subject. Increases or decreases to the dose of UCB0942 should be made in steps not exceeding 200mg/day per week; an exception is Taper Week 1 where a step of 800mg/day to 500mg/day is allowed. A faster decrease of the dose than 200mg/day per week is allowed when it is clinically appropriate in the Investigator's medical judgment. Daily UCB0942 doses during this study may be 100mg (50mg bid), 200mg (100mg bid), 400mg (200mg bid), 600mg (300mg bid), or 800mg (400mg bid); intermediate doses will not be allowed except for tapering and titration unless agreed by the **PRA Medical Monitor**. The dose of UCB0942 must always be administered as bid morning and evening doses, approximately 12 hours apart. The first dose of the current study will be the dose on the evening of V2.

Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. The **PRA Medical Monitor** must be consulted prior to initiation of concomitant AED withdrawal. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction, if the concomitant medication has been approved for focal seizures by the health authority of the subject's country of residence, taking the drug-to-drug interactions profile of UCB0942 into account. New AEDs (with the exception of AEDs listed in the prohibited medication section, Section 7.8.2) should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of UCB0942.

Change #13

Section 7.3 Packaging

UCB0942 tablets will be provided in bottles, containing 135 tablets for the 25mg dosage and either 80 or 200 tablets for both the 100mg and 200mg dosage. Appropriate bottle size will be dispensed through the IRT system as per visit schedule and visit interval.

Has been changed to:

UCB0942 tablets are manufactured, packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way to protect the IMP from deterioration during transport and storage. Packaging details are included in the IMP Handling Manual.

Change #14

Section 7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of UCB0942 at the site. Investigational medicinal product stored by the Investigator (or designee) is to be kept in a secured area with limited access.

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

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) and feedback must be received before further use of UCB0942.

The CPM (or designee) will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature) to the Clinical Supply Manager. Based on discussion with a UCB Quality Assurance representative, the Clinical Supply Manager will then provide the CPM (or designee) with instructions for the site regarding the use of UCB0942.

The Investigator (or designee) will instruct the subject to store UCB0942 following the instructions on the label.

Has been changed to:

TheInvestigator (or designee) is responsible for the safe and proper storage of UCB0942 at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (ie, every working day), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions and IMP information contained in the IMP Handling Manual. The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

Change #15

Section 7.8.1 Permitted concomitant treatments (medications and therapies), first bullet

- All subjects will enter EP0073 using their current AED regimen. Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject. Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to optimize tolerability and seizure reduction. Changes in AEDs should be discussed with the UCB Study Physician or PRA Medical Monitor on an individual and case-by-case basis.

Has been changed to (change bolded):

- All subjects will enter EP0073 using their current AED regimen. Concomitant AEDs and AED dose(s), or VNS settings may be adjusted throughout EP0073 as per the Investigator's clinical judgment based on tolerability and seizure control for each individual subject. Concomitant AED(s) may be carefully tapered and discontinued to achieve UCB0942 monotherapy, if clinically appropriate. New concomitant AEDs may be introduced to

optimize tolerability and seizure reduction. Changes in AEDs should be discussed with the **PRA Medical Monitor** on an individual and case-by-case basis.

Change #16

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study (this is not a complete list of prohibited medications):

- Carbamazepine, phenytoin, phenobarbital, primidone, or other AEDs that are strong CYP3A4 inducers
- Benzodiazepines taken >3 times per week (ie, >3 doses within 7 days)
- Zolpidem, zaleplon, or zopiclone taken >3 times per week
- Tiagabine
- Felbamate
- Vigabatrin
- Strong non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

Has been changed to (change bolded):

The following concomitant medications are prohibited during the study (this is not a complete list of prohibited medications):

- Carbamazepine, phenytoin, phenobarbital, primidone, or other AEDs that are strong CYP3A4 inducers
- Benzodiazepines taken >3 times per week (ie, >3 doses within 7 days)
- Zolpidem, zaleplon, or zopiclone taken >3 times per week
- Tiagabine
- Felbamate
- Vigabatrin
- Strong non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

The following medications* should not be administered concomitantly with UCB0942. However, if subjects are already taking these medications prior to Amendment 3, they may continue to do so, but close monitoring should be implemented.

- **Strong CYP2C19 inhibitors (eg, fluconazole, fluoxetine, fluvoxamine, and ticlopidine)**

- **Strong CYP2C19 inducers (eg, including rifampicin and ritonavir)**
- **CYP2C19 sensitive substrates (eg, s-mephenytoin and omeprazole)**

***For more details refer to Table 3-1, Table 3-2, and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitor and inducers.**

Change #17

Section 8.2.3 Minimal Evaluation Visit, echocardiogram assessments

- Echocardiogram (not at V3)

Has been changed to (change bolded):

- Echocardiogram (not at V3, **V14, and V16**)

Change #18

Section 11.1.8 Safety signal detection, third paragraph

Any findings from this review will be brought to the attention of the DMC, that will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship with new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to study procedures, withdrawal or limiting inclusion of subjects with a negative benefit-risk balance, or termination of the clinical study. The precise membership, scope, and responsibilities of the DMC are described in the DMC Charter.

Has been changed to (change bolded):

Any findings from this review will be brought to the attention of the DMC, that will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship with new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within approximately 3 months after first dosing in EP0073. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist. The DMC will make recommendations to the company about continuation of the study, which may include changes to **study procedures, or termination** of the clinical study. The precise membership, scope, and responsibilities of the DMC are described in the DMC Charter.

Change #19

Section 11.3 Adverse events of special interest, a link to the section describing PDILI has been added

Guidance on the evaluation and management of PDILI is provided in Section 11.6.1.

Change #20

Section 11.4 Immediate reporting of adverse events, adverse events of special interest has been added

- Adverse events of special interest (see Section 11.3)

Change #21

Section 11.7.3 Echocardiogram, paragraph after numbered list

Images will be recorded and stored digitally and retained if further analysis is needed. Central reading of the echocardiograms may be performed by a specialized vendor.

Has been changed to (change bolded):

Images will be recorded and stored digitally and retained if further analysis is needed. **In the event that echocardiograms are not interpretable during the study, alternative assessments using either transesophageal echocardiography or cardiac magnetic resonance imaging (CMR) should be performed.** Central reading of the echocardiograms may be performed by a specialized vendor.

Change #22

Section 11.7.8 Narratives of benefit and benefit-risk assessment

Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form during the Screening Period and at other scheduled time points presented in Table 5-2. The verbatim of the attained benefits or treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be recorded as narratives by the Investigator or site personnel. The Investigator will also assess and provide a brief justification that the benefit-risk ratio for the subject of the long-term treatment with the IMP remains positive, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options.

Has been changed to (change bolded):

Narratives of benefit by the subject/caregiver and the benefit-risk statement and the justification by the Investigator will be captured in a dedicated form during the Screening Period and at other scheduled time points presented in Table 5-2. The verbatim of the attained benefits or treatment with UCB0942, including seizure control, health and well-being, and social functioning, declared by a subject/caregiver will be recorded as narratives by the Investigator or site personnel. The Investigator will also assess and provide a brief justification that the benefit-risk ratio for the subject **on** long-term treatment with the IMP **supports continuation in the study**, considering the knowledge of the IMP's efficacy and safety profile and alternative treatment options.

Change #23

Section 12.4 Termination of the study, first paragraph

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, negative benefit-risk balance, or unsatisfactory enrollment with respect to quality or quantity.

Has been changed to (change bolded):

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, benefit-risk balance **(0 to 4) indicating the risks outweigh the benefits,** or unsatisfactory enrollment with respect to quality or quantity.

Change #24

Section 13.1 Definition of analysis sets, PK analysis set has been added

The Pharmacokinetic Per-Protocol Set will consist of subjects in the FAS who received at least 1 dose of study medication, and did not have a major protocol deviation impacting the PK variables.

Change #25

Section 13.8 Planned interim analysis and data monitoring, first and second paragraphs

A DMC will systematically monitor and report (at least quarterly up to the time point when the last patient entering EP0073 reaches 1 year in the study, and less frequent thereafter) on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC approximately 3 months after first dosing in EP0073. Blinded data until database lock from EP0069 and data from the OLE EP0073 studies will be reviewed in order for the DMC to provide an ongoing risk-benefit evaluation with particular reference to the occurrence of psychiatric and cardiological/cardiovascular AEs, seizure control, and any new identified safety signals. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist, none of whom will be involved with the conduct of the study, either by management or participation. In addition, there will be an independent reporting team, consisting of an independent statistician and independent statistical programmers, who will be completely independent from the blinded reporting team. The blinded reporting team will be responsible for all operational aspects of the study, including routine monitoring and cleaning of the data, programming, and quality control of all analyses defined in the interim EP0073 SAP on blinded data of EP0069 and unblinded data of EP0073 (open-label study). If required for monitoring of safety and benefit-risk of EP0073 patients, unblinded data from EP0069 study can be reviewed by the external members of the DMC at closed sessions and provided by an independent statistician. The DMC will make recommendations to the company, which may

include changes to study procedures, withdrawal of subjects with a negative risk balance, or termination of the clinical study.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be followed to maximize subject safety and ensure positive benefit-risk balance of participation in the study.

Has been changed to (change bolded):

A DMC will systematically monitor and report (at least quarterly up to the time point when the last patient entering EP0073 reaches 1 year in the study, and less frequent thereafter) on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for IMP efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC approximately 3 months after first dosing in EP0073. Blinded data until database lock from EP0069 and data from the OLE EP0073 studies will be reviewed in order for the DMC to provide an ongoing risk-benefit evaluation with particular reference to the occurrence of psychiatric and cardiological/cardiovascular AEs, seizure control, and any new identified safety signals. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist, none of whom will be involved with the conduct of the study, either by management or participation. In addition, there will be an independent reporting team, consisting of an independent statistician and independent statistical programmers, who will be completely independent from the blinded reporting team. The blinded reporting team will be responsible for all operational aspects of the study, including routine monitoring and cleaning of the data, programming, and quality control of all analyses defined in the interim EP0073 SAP on blinded data of EP0069 and unblinded data of EP0073 (open-label study). If required for monitoring of safety and benefit-risk of EP0073 patients, unblinded data from EP0069 study can be reviewed by the external members of the DMC at closed sessions and provided by an independent statistician. The DMC will make recommendations to the company, which may include changes to **study procedures, or termination** of the clinical study.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be followed to maximize subject safety and ensure **that the** benefit-risk balance **justifies** participation in the study.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

19 DECLARATION AND SIGNATURE OF COORDINATING INVESTIGATOR (GERMANY)

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Coordinating Investigator (Germany):

[redacted]

_____

Date/Signature

20 DECLARATION AND SIGNATURE OF COORDINATING INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Coordinating Investigator:

[redacted]

_____

Date/Signature

21 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.

EP0073 Protocol Amendment 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	14-Nov-2017 15:57 GMT+0
[redacted]	Clinical Approval	14-Nov-2017 15:59 GMT+0