
PROTOCOL EP0092

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PADSEVONIL AS ADJUNCTIVE TREATMENT OF FOCAL-ONSET SEIZURES IN ADULT SUBJECTS WITH DRUG-RESISTANT EPILEPSY

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
bid	twice daily
BP	blood pressure
BZD	benzodiazepine
cBZR	central benzodiazepine receptor
CDMS	clinical data management system
CI	confidence interval
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
CNS	central nervous system
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EDV	Early Discontinuation Visit
EEG	electroencephalogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	first patient first visit
GABA-A	gamma-aminobutyric acid-A
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HDRE	highly drug-resistant epilepsy
HRU	healthcare resource utilization
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
LEV	levetiracetam
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
OLE	open-label extension
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PET	positron-emission tomography
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-Protocol Set
PRN	(pro re nata) as needed
PS	Patient Safety
PSL	padsevonil
QOLIE-31-P	Quality of Life Inventory in Epilepsy-31-P
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure

SD	standard deviation
SFU	Safety Follow-Up
SOP	Standard Operating Procedure
SS	Safety Set
SSG	Seizure Severity Global Item
SUDEP	sudden unexpected death in epilepsy
SV2	synaptic vesicle 2
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
TTE	transthoracic echocardiogram
ULN	upper limit of normal
VNS	vagus nerve stimulation

1 SUMMARY

Padsevonil (PSL) is a novel chemical entity that has selective affinity for both presynaptic synaptic vesicle 2 (SV2) proteins and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid-A (GABA-A) receptor. Specifically synthesized and designed for an increased anticonvulsant activity, PSL has the potential to benefit an underserved population with high unmet medical need, namely those with drug-resistant epilepsy and uncontrolled focal-onset seizures that constitute substantial threats to their health and well-being.

EP0092 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults (≥ 18 years of age) with drug-resistant epilepsy who continue to have uncontrolled focal-onset seizures despite treatment with at least 4 tolerated, appropriately chosen and used prior antiepileptic drugs (AEDs), including current AEDs (Kwan et al, 2010).

The primary objective of this study is to evaluate the efficacy of the 3 selected dose regimens of PSL administered concomitantly with up to 3 AEDs compared with placebo for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy. The secondary objective is to assess the safety and tolerability of all doses of PSL in relation to placebo.

The study comprises the following periods: a 4-week Baseline Period; a 16-week Treatment Period consisting of a 3-week Titration Period followed by a 1-week Stabilization Period and a 12-week Maintenance Period; a 3-week Conversion Period for all subjects who choose to enroll in the open-label extension (OLE) study, EP0093, at the end of the Maintenance Period; or a 4-week Taper Period, in case the subjects discontinue or do not enroll in EP0093. During the Titration Period, the investigational medicinal product (IMP) will be increased approximately every 3 to 7 days depending on the treatment arm. For subjects with tolerability issues at their target dose, 1 fallback option to a predefined lower dose will be allowed during the Stabilization Period. During the entire 12-week Maintenance Period, the dose of IMP and concomitant AEDs must remain stable. Subjects who withdraw from the study or decide not to participate in the OLE study will be progressively tapered off the IMP. Safety follow up for these subjects will consist of 1 Safety Follow-up (SFU) Visit 30 days after the last IMP intake (including an echocardiogram) and a 6-month follow-up echocardiogram, depending on the duration of exposure to IMP.

The assessment of efficacy is based on seizure frequency. For the US Food and Drug Administration (FDA), Pharmaceuticals and Medical Devices Agency (PMDA), Chinese FDA, and other regulatory authorities not specified in Section 4.1.1.2, the primary efficacy variable is the change from Baseline in log-transformed observable focal-onset seizure frequency (for the purpose of this protocol defined as Types IA1, IB, and IC, according to the International League Against Epilepsy [ILAE] classification [ILAE Classification of Epileptic Seizures, 1981]) over the 12-week Maintenance Period. For the European Medicines Agency (EMA) and regulatory authorities who reference EMA, the primary efficacy variable is the 75% responder rate, where a responder is a subject experiencing a $\geq 75\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period.

Secondary and other efficacy variables will allow further exploration of the effect of PSL on seizure frequency during the entire Treatment Period, seizure severity, quality of life, Hospital Anxiety and Depression Scale (HADS) score, health-related outcomes, and healthcare resource utilization (HRU). Safety will be evaluated based on the occurrence of adverse events (AEs)

reported by the subject and/or caregiver; subject withdrawals or premature tapering due to AEs; the results of periodic clinical laboratory evaluations, electrocardiograms (ECGs), echocardiograms, withdrawal symptom monitoring, vital sign monitoring; and physical and neurological examinations.

The total duration of the study per subject will be up to 27 weeks with a maximum of 19 weeks exposure to PSL. It is estimated that approximately 555 subjects will be enrolled at approximately 200 sites worldwide (approximately 500 subjects in Europe/North America/Japan and at least 55 subjects in China); approximately 444 subjects are expected to be randomized (approximately 400 subjects in Europe/North America/Japan and at least 44 subjects in China).

An independent Data Monitoring Committee (DMC) has been formed for EP0091 and EP0093; the same DMC will monitor the ongoing safety of this study.

2 INTRODUCTION

2.1 Drug-resistant epilepsy

The ILAE defines drug resistance as failure of adequate trials of at least 2 tolerated and appropriately chosen AEDs, either as monotherapy or in combination, to achieve sustained seizure freedom (Kwan et al, 2010). In the US, there are 3 million adults with active epilepsy (Zack and Kobau, 2017). Assuming epilepsy with focal-onset seizures in 60% of patients and resistance to AEDs in 20% to 40% of patients, approximately 360,000 to 720,000 patients suffer from drug-resistant epilepsy (Giussani et al, 2016; Kwan and Sander, 2004; Semah et al, 1998). It is this drug-resistant epilepsy population that represents the greatest burden of disease for individuals, physicians, and the healthcare system. A treatment that provides a significant reduction in seizure frequency will reduce mortality and significantly improve quality of life.

In patients with drug-resistant epilepsy, seizures have a negative impact on mortality, psychosocial functioning, and quality of life across multiple domains. Patients with resistant, focal epilepsy and complex partial or tonic-clonic seizures have a 5 to 10 times higher mortality rate (Fazel et al, 2013; Hesdorffer and Tomson, 2013; Holst et al, 2013; Sperling, 2004), including a risk of sudden unexpected death in epilepsy (SUDEP) (Devinsky, 2011) when compared with the general population. An estimated 1% of patients diagnosed with drug-resistant epilepsy die every year of SUDEP (Jehi, 2016). Moreover, 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, cannot drive, can rarely live independently, feel isolated and stigmatized, 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). It is well known that even with the development of several AEDs in the recent past, the proportion of patients with epilepsy who are able to achieve complete control of their seizures has only increased minimally, from 64% to 68% (Brodie et al, 2012).

Moreover, it is important to highlight that there is a continuum of drug resistance within the population classified as drug-resistant according to ILAE criteria. The likelihood of achieving complete seizure control diminishes as the number of failed AED regimens increases. When a patient with drug-resistant epilepsy has failed to achieve seizure freedom with the second AED regimen, he or she has a 10% chance of achieving complete seizure control with subsequent AED regimens (Steinhoff, 2014; Beyenburg et al, 2012; Chung et al, 2010a; Schiller and Najjar, 2008; Mohanraj and Brodie, 2006).

Although effective pharmacologic treatment options are limited for this patient population, some patients may benefit from surgical options. Resective surgery may provide long-term (up to 5 years) seizure freedom in up to 52% of patients (de Tisi et al, 2011). Surgery is associated with several risks, both those inherent to surgery (infection, bleeding) and those specific to resective epilepsy surgery (loss of function after removal of brain tissue). The ILAE recommends that patients with focal epilepsy be evaluated for surgery after failing to achieve seizure freedom with the second AED regimen; however, in most European and North American countries, patients are referred for surgery only after failing multiple AED regimens (Engel, 2013). Due to various factors (limited number of epilepsy surgery centers, inability to localize the seizure focus, surgical contraindications, etc) only a small percentage of patients meeting ILAE recommendations are evaluated for surgery (Engel, 2013). Therefore, the vast majority of patients with drug-resistant, focal epilepsy have no treatment options – pharmacological or surgical – that can provide complete seizure control or a clinically meaningful reduction in the number of seizures.

A treatment that provides a significant reduction in seizure frequency will reduce mortality (Laxer et al, 2014) and significantly improve quality of life (Choi et al, 2014; Baker et al, 1997) by increasing patients' ability to attain basic safety, have 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, having a productive and rewarding profession, or other means of self-realization.

2.2 Padsevonil mechanism of action

Padsevonil is a novel chemical entity that has selective affinity both for presynaptic SV2 proteins and for postsynaptic cBZR sites on the GABA-A receptor. At presynaptic sites, PSL binds with high affinity to all 3 subtypes of the human SV2 protein (ie, SV2A, SV2B, and SV2C), and at postsynaptic sites acts as a partial agonist, binding with moderate affinity to the cBZR sites. Whereas SV2A ligands are characterized by broad-spectrum anticonvulsant activity, GABA-A receptors mediate inhibitory neurotransmission, and their allosteric modulation by cBZR site offers robust protection against seizures. The synergistic anticonvulsive effect observed when combining levetiracetam (LEV) with benzodiazepines (BZDs) in preclinical models (Kaminski et al, 2009) was the motivation that led to the design of PSL.

In nonclinical studies, PSL has shown higher potency than LEV combined with a BZD (diazepam) at matching in vivo occupancies of SV2A and cBZR, respectively. This suggests that PSL's preclinical potency is not only due to the combination of these 2 precedented mechanisms of action, but that a unique interaction of PSL with SV2 proteins may also play a role.

Preclinical experience with PSL is described extensively in the Investigator's Brochure (IB).

2.3 Clinical studies

To date, PSL has been administered in the following 9 completed human pharmacology studies:

- N01360—a single, ascending dose safety, pharmacokinetic (PK), and pharmacodynamics (PD) study
- N01386—a multiple, ascending dose safety, PK, and PD study
- UP0010—a single-dose absorption, distribution, metabolism, and elimination study

- UP0001—a single- and multiple-dose comparative PK and food effect study
- UP0013—a multiple-dose, 2-part drug-drug interaction (DDI) study
- N01383—a positron-emission tomography (PET) study evaluating the brain GABA-A receptor occupancy following multiple dosing of PSL
- UP0002—a multiple-dose study in subjects with epilepsy investigating the effect of PSL on the PK of carbamazepine epoxide and the PK, safety, and tolerability of PSL in the presence of concomitant AEDs
- UP0036—an adaptive, open-label, single-dose PET study evaluating SV2A occupancy
- UP0039—a single- and multiple-dose safety and PK study in healthy Japanese and Caucasian subjects

There are also 2 ongoing Phase 1 clinical pharmacology studies: UP0057, an open-label, fixed-sequence study in healthy subjects evaluating the effect of co-administered erythromycin on the PK and safety of PSL; and UP0070, a multicenter, open-label, parallel-group study in subjects with epilepsy evaluating the effect of oxcarbazepine on the PK, safety, and tolerability of PSL.

In addition, the following Phase 2 studies have been performed: EP0069, EP0073 (ongoing), and EP0091 (ongoing), as well as one Phase 2/3 OLE study, EP0093 (ongoing). EP0069 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study; and EP0073 is a multicenter OLE to evaluate the long-term safety, tolerability, and efficacy of PSL when used as adjunctive therapy for partial-onset seizures in adult subjects with highly drug-resistant focal epilepsy. The subjects who enrolled in the Phase 2 study, EP0069, and OLE study, EP0073, had highly drug-resistant epilepsy (HDRE) which was defined in these studies as subjects who had ≥ 4 focal seizures, with or without secondary generalization, per week and who had failed to achieve seizure control with ≥ 4 AED regimens of adequate dose and duration. Patients with HDRE are considered to be a subset of the drug-resistant epilepsy population, the patient population for the registration program including EP0091 and EP0093, as well as the current study, EP0092.

In the Phase 2 proof of concept study, EP0069, a total of 55 subjects were randomized to receive placebo or PSL titrated up to 400mg twice daily (bid) for a 2-week Inpatient Period administered concomitantly with each subject's current and stable AED regimen. In the placebo arm, the 2-week inpatient placebo treatment was followed by up-titration to PSL 400mg bid in Week 3. All subjects continued on PSL in an 8-week open-label Outpatient Period. The primary objective of the study was to evaluate the efficacy of PSL compared with placebo, administered concomitantly with each subject's current, stable AED regimen. Adjunctive therapy with PSL was associated with clinically meaningful improvements in seizure frequency in adult patients with highly drug-resistant focal epilepsy and frequent seizures compared with placebo. Three subjects ($n=3/27$) (11.1%) in the placebo/PSL treatment group and 8 subjects ($n=8/26$) (30.8%) in the PSL/PSL treatment group had a $\geq 75\%$ reduction from the Baseline Period in focal seizure frequency during the 2-week Inpatient Period. The 75% responder rate approached statistical significance ($p=0.0679$) and was clinically meaningful. The median percent reduction in weekly focal seizure frequency from Baseline to the 2-week Inpatient Period in the PSL/PSL treatment group (53.68%) was greater than in the placebo/PSL treatment group (12.50%). The

median difference vs placebo for the PSL treatment group was 34.0% (95% confidence interval [CI]: 3.0, 67.5). Secondary analyses demonstrated the maintenance of effect during the Outpatient Period, last 4 weeks of the Outpatient Period, and on-PSL treatment overall. Additional details regarding the efficacy can be found in the IB.

A total of 42 subjects have been enrolled in EP0073, the OLE study to EP0069.

EP0091 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose finding study to evaluate the efficacy and safety of PSL as adjunctive treatment of focal-onset seizures in adult subjects with drug-resistant epilepsy. EP0093 is an open-label, multicenter, extension study to evaluate the safety and efficacy of PSL as adjunctive treatment of focal-onset seizures in adult subjects with drug-resistant epilepsy. Subjects can enroll into EP0093 from previously completed studies, including the current study, EP0092. EP0091 and EP0092 will be the 2 adequate and well-controlled studies to support the registration filing of PSL as adjunctive treatment of focal-onset seizures in adult subjects with drug-resistant epilepsy.

2.3.1 Adverse event profile

In general, in EP0069, there were no new or unexpected safety signals. The most frequently reported treatment-emergent adverse events (TEAEs) for subjects overall were somnolence, dizziness, headache, fatigue, and irritability. Overall, the most frequently reported TEAEs considered drug-related by the Investigator were somnolence, dizziness, and fatigue. Four serious TEAEs were reported for 2 subjects (1 subject had a serious TEAE of status epilepticus and 1 subject had serious TEAEs of impaired judgment, delirium, and dysphoria) during the On-PSL Overall Period. There were no deaths reported during the study. During the On-PSL Overall Period, in the 18 subjects who reported TEAEs leading to a dose reduction of PSL, the most common TEAEs were dizziness, somnolence, and fatigue. One subject withdrew from the study due to TEAEs of dysphoria and mood swings. There was no evidence for any consistent effect on laboratory parameters, vital signs, weight, ECG evaluations, physical examinations, or neurological examinations in the overall population. Based on the study results, treatment with PSL was generally well tolerated, with an acceptable tolerability and safety profile pointing to an overall positive benefit/risk balance.

No subjects have completed the OLE study (EP0073). As of June 2018, 18 subjects (42.9%) had discontinued.

In summary, in the Phase 1 program 181 healthy subjects and 20 patients with epilepsy (male and female) have been exposed to PSL at single doses up to 490mg (58 healthy volunteers) and repeated doses up to 400mg bid for up to 12 days (123 healthy subjects and 20 patients) in completed studies. In the Phase 2 proof of concept study (EP0069), 55 subjects were exposed at doses up to 400mg bid during the maintenance phase of the study. A total of 42 of the 55 subjects enrolled in the OLE study, during which they were allowed to adjust their PSL dose.

The safety findings to date suggest that the AEs experienced by subjects receiving single and repeated doses of PSL are limited principally to central nervous system (CNS) effects and that these are consistent with the known pharmacology of PSL, ie, similar to AEs associated with other SV2A- and GABA-A-targeting AEDs. The AEs tend to be dose-related in frequency and intensity, self-limiting, and tend to decrease in intensity over the first few days of dosing.

The psychiatric findings currently reported are consistent with the AE profile of other AEDs, including other SV2A ligands. Acute psychiatric effects occurred in 3 subjects administered PSL (2 in Phase 1 and 1 in Phase 2a). The events were transient, acute, and required admission to psychiatric care and antipsychotics. No definite dose relationship could be determined, and the events occurred after variable periods of time following the first administration of the IMP. Some new AEs (mainly headache and sleep disturbance) developed after dose discontinuation with PSL in the Phase 1 studies, indicating a potential withdrawal syndrome. These have been mild, transient, not dose-related, and not of clinical concern. The occurrence of these behavioral AEs highlights the need to consider the possibility of and maintain vigilance for significant psychiatric AEs.

With regard to cardiovascular effects, minor, transient reductions in blood pressure (BP) were observed in the Phase 1 and Phase 2 studies; however, these were not clinically meaningful and resolved without intervention. The degrees of reduction seen in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are consistent with the GABA-A-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use (Jones et al, 1979). In regard to ECG results, all nonclinical and clinical Phase 1 and Phase 2 cardiac data in totality were reviewed by an expert cardiologist consultant whose opinion was that “overall, there is no clear evidence that PSL is associated with any increase in incidence of ectopy, change in QTc interval, or clinically significant arrhythmia in clinical trials to date”. Echocardiographic screening of subjects at Baseline (to exclude subjects with valvulopathies) and ongoing echocardiographic monitoring during treatment and posttreatment has been implemented in the Phase 2 studies. No major findings were observed in EP0069 or have been observed in the ongoing OLE study, EP0073. Cardiac monitoring (eg, ECGs, vital signs, echocardiograms) is planned throughout the duration of the development program in order to better understand and mitigate any risks.

In general, the safety profile has been consistent with the pharmacological properties of the drug and consistent with studies of AEDs in regards to the type and severity of nervous system and psychiatric AEs reported, with most AEs reported as mild or moderate. The overall safety profile during the clinical program to date can be found in the IB.

2.4 Rationale for this study

With over 25 AEDs approved (15 in the last 15 years), the majority of patients with epilepsy and focal-onset or focal to bilateral tonic-clonic (previously called “secondary generalized”) seizures have options for effective monotherapy and/or combination therapies early in the treatment paradigm; however, none of the options differentiate by superior efficacy. Seizure control has only changed marginally even with the latest new AED treatments (Brodie et al, 2012) and for the majority of severely affected and drug-resistant patients, there are few, if any, treatment options remaining.

Padsevonil is an AED with a dual mechanism of action, specifically synthesized and designed for increased anticonvulsant activity and hence for the treatment of seizures in patients with epilepsies resistant to currently available drug therapies. Based on the evidence of superior seizure control compared with other marketed AEDs across several preclinical models of epilepsy and the results of the proof of concept study, EP0069, treatment with PSL has the potential to benefit an underserved epilepsy population with high unmet medical need, namely those who have drug-resistant epilepsy whose uncontrolled focal-onset seizures constitute a

substantial threat to their health and well-being. The current study, EP0092, will evaluate the efficacy and safety of 3 dose regimens of PSL administered concomitantly with up to 3 AEDs compared with placebo for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective is to evaluate the efficacy of the 3 selected dose regimens of PSL administered concomitantly with up to 3 AEDs compared with placebo for treatment of observable focal-onset seizures in subjects with drug-resistant epilepsy.

3.2 Secondary objective

The secondary objective is to assess the safety and tolerability of PSL in relation to placebo.

3.3 Other objectives

3.3.1 Efficacy objectives

The other efficacy objective is to assess HRU and quality of life.

3.3.2 Pharmacokinetic objectives

The PK objectives are to:

- Evaluate the steady-state PK of PSL
- Evaluate the impact of enzyme-inducing concomitant AEDs on PSL exposure
- Evaluate concomitant AED (and/or relevant metabolites) plasma levels

4 STUDY VARIABLES

4.1 Efficacy variables

Seizure frequency refers to 28-day adjusted frequency. Observable focal-onset seizures refer to focal aware (Type IA1), focal unaware (Type IB), and focal to bilateral tonic-clonic (Type IC) seizures (ILAE Classification of Epileptic Seizures, 1981). Focal-onset seizures include all Type I seizures. Seizure-free status and seizure-free days include all (Types I, II, and III) seizure types.

4.1.1 Primary efficacy variable

4.1.1.1 Primary efficacy variable for the US FDA, PMDA, Chinese FDA, and other regulatory authorities not specified in Section 4.1.1.2

The primary efficacy variable is the change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period.

4.1.1.2 Primary efficacy variable for EMA and regulatory authorities who reference EMA

The primary efficacy variable is the 75% responder rate, where a responder is a subject experiencing a $\geq 75\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period.

4.1.2 Secondary efficacy variables

4.1.2.1 Secondary efficacy variables for the US FDA, PMDA, Chinese FDA, and other regulatory authorities not specified in Section 4.1.2.2

The secondary efficacy variables are as follows:

- The 75% responder rate, where a responder is a subject experiencing a $\geq 75\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- The 50% responder rate, where a responder is a subject experiencing a $\geq 50\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

4.1.2.2 Secondary efficacy variables for EMA and regulatory authorities who reference EMA

The secondary efficacy variables are as follows:

- The change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- The 50% responder rate, where a responder is a subject experiencing a $\geq 50\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period
- Percent reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

4.1.3 Other efficacy variables (this list applies for all regulatory authorities)

The other efficacy variables are as follows:

- Change from Baseline in log-transformed observable focal-onset seizure frequency over the first 4 weeks, second 4 weeks, and third 4 weeks of the 12-week Maintenance Period
- Change from Baseline in log-transformed observable focal-onset seizure frequency over the 16-week Treatment Period
- The 50% responder rate, where a responder is a subject experiencing a $\geq 50\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period
- The 75% responder rate, where a responder is a subject experiencing a $\geq 75\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period
- The 90% responder rate, where a responder is a subject experiencing a $\geq 90\%$ reduction in observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period

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- Percent reduction in observable focal-onset seizure frequency from Baseline, over the 16-week Treatment Period
 - Change from Baseline in log-transformed focal-onset (Type I) seizure frequency over the 12-week Maintenance Period
 - The 50% responder rate, where a responder is a subject experiencing a $\geq 50\%$ reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period
 - The 75% responder rate, where a responder is a subject experiencing a $\geq 75\%$ reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period
 - The 90% responder rate, where a responder is a subject experiencing a $\geq 90\%$ reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period
 - Percent reduction in focal-onset (Type I) seizure frequency from Baseline, over the 12-week Maintenance Period and the 16-week Treatment Period
 - Seizure-freedom status (“Yes”/“No”) during the 12-week Maintenance Period and the 16-week Treatment Period
 - Number of seizure-free days during the 12-week Maintenance Period and the 16-week Treatment Period
 - Cumulative responder rate during the 16-week Treatment Period
 - Change in the Seizure Severity Global Item (SSG) scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and the end of the 16-week Treatment Period (Visit 7)
 - Change in Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P) scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and the end of the 16-week Treatment Period (Visit 7)
 - Change in HADS scores from Baseline to Week 4 during the Maintenance Period (Visit 4) and to the end of the 16-week Treatment Period (Visit 7)
 - Time to return to Baseline observable focal-onset seizure frequency during the 12-week Maintenance Period
 - Use of health-related outcomes and HRU, including healthcare provider consultations not foreseen by protocol, caregiver support, concurrent medical procedures, concomitant medications, and hospitalizations

4.2 Safety variables

4.2.1 Primary safety variables

The safety variables are as follows:

- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during the entire study
- Incidence of TEAEs leading to study withdrawal
- Incidence of treatment-emergent serious adverse events (SAEs) during the entire study

4.2.2 Other safety variables

Other safety variables are as follows:

- Incidence of TEAEs reported by the subject and/or caregiver or observed by the Investigator during the following periods: 16-week Treatment Period, 12-week Maintenance Period, 4-week Titration/Stabilization Period, and 3-week Taper Period
- Number of and reason for subjects requiring premature tapering due to TEAEs
- Number of and reason for subjects requiring a dose reduction during the Stabilization Period due to TEAEs
- Incidence of treatment-emergent SAEs during the following periods: 16-week Treatment Period, 12-week Maintenance Period, 4-week Titration/Stabilization Period
- Changes in clinical laboratory test parameters (including hematology, blood chemistry, and urinalysis)
- Changes in vital sign parameters (including pulse rate, SBP, DBP, and respiratory rate)
- Changes in 12-lead ECG parameters
- Physical examination (including body weight) and neurological examination findings
- Changes in Psychiatric and Mental Status exam
- Occurrence of valvular abnormalities or pericardial effusion changes or other significant abnormalities as identified by 2-dimensional Doppler echocardiogram at each assessment by central reader
- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) from the end of the 16-week Treatment Period (Visit 7) to the end of the Taper Period (Visit 8) and the end of the SFU Period (Visit 9 [30 days after the last IMP intake])

4.3 Other variables

4.3.1 Pharmacokinetic variables

Blood concentrations of PSL will be determined from samples obtained in the study during the Treatment Period in order to investigate the following variable:

- The population PK profiles of PSL

Blood concentrations of concomitantly administered AEDs will also be evaluated for evidence of DDIs with PSL at steady state.

Comparison may be made between blood concentration data of PSL and desmethyl metabolite derived from the volumetric absorptive microsampling MITRA[®] technology.

Additionally, evaluation of PSL and desmethyl metabolite in plasma may be undertaken from trough samples. The collection of plasma samples for this comparison may cease during the course of the study based on periodic review of the data.

5 STUDY DESIGN

5.1 Study description

EP0092 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults (≥ 18 years of age) with drug-resistant epilepsy who continue to have uncontrolled focal-onset seizures despite treatment with at least 4 prior AEDs, including current AEDs. All eligible subjects will have an epilepsy diagnosis and at least 4 observable focal-onset seizures per 28 days despite treatment with at least 1 to 3 AEDs, with or without neurostimulation devices at stable regimens, with doses and settings individually optimized for efficacy and safety/tolerability.

Subjects should be educated to complete their diary entries accurately as per instruction.

The study is composed of 4 periods (see [Figure 5-1](#) for a schematic diagram):

Baseline Period (4 weeks)

During the Screening Visit (Visit 1, Week -4), subjects will sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure or pretreatment assessments, and the subject's eligibility will be determined on the basis of the inclusion/exclusion criteria. Subject eligibility related to seizure frequency will be evaluated based on Investigator assessment of the subject report on historical seizure count during the 8 weeks prior to the Screening Visit (Visit 1) for the retrospective seizure baseline. Eligible subjects will be given a diary and receive instructions to further document seizures during the 4-week Baseline Period for a prospective seizure baseline. All subjects must have been on a stable dose of their current AEDs during the 8 weeks prior to the Screening Visit (Visit 1). For the neurostimulation device (if applicable), the settings should be stable for 12 weeks prior to the Screening Visit (Visit 1). Both should be stable throughout the study until the end of the Treatment Period. The Investigator will be asked to send documentation of a video-electroencephalogram (EEG) report, as per instruction, to the UCB Study Physician or representative for confirmation of eligibility before randomization of the subject.

Treatment Period (16 weeks)

The 16-week Treatment Period includes a 3-week Titration Period followed by a 1-week Stabilization Period and a 12-week Maintenance Period. Four weeks after the Screening Visit (Visit 1), subjects will return to the clinic for the Baseline Visit (Visit 2, Day 1). Subjects who continue to fulfill the inclusion and exclusion criteria will be randomized to 1 of the 4 treatment arms in a 1:1:1:1 ratio (using random permuted blocks to ensure balanced randomization across the 4 treatment arms). Randomization will be stratified by current use of AEDs that bind to SV2A proteins (LEV or brivaracetam) and by region (Europe, North America, Japan, and China) at the time of randomization.

During the entire 16-week Treatment Period, the dose of concomitant AEDs and the settings for neurostimulation devices must remain stable.

After the Baseline Visit (Visit 2), regular visits will be scheduled for the remainder of the Treatment Period.

Titration Period (3 weeks)

Investigational medicinal product will be increased approximately every 3 to 7 days depending on treatment arms (refer to [Table 7-1](#) for details). Subjects will be instructed to take the IMP in 2 equally divided doses, approximately 12 hours apart in the morning and evening.

Subjects who cannot tolerate IMP through Week 3 will be withdrawn from the study.

Stabilization Period and fallback (1 week)

Subjects who tolerate IMP will continue with their target dose throughout the Stabilization Period. For subjects with tolerability issues at their target dose, one fallback to a predefined dose based on the randomized dose ([Table 7-2](#)) will be allowed during the Stabilization Period and should occur at least 2 days prior to the start of the Maintenance Period (Visit 4) for subjects who experience tolerability issues during Week 4. The Study Physician or delegate should be consulted prior to use of the fallback option and the date as well as the reason for fallback will be recorded in the source documents and in the electronic Case Report form (eCRF).

Fallback may be managed via an unscheduled visit. Fallback IMP packs will be allocated via the interactive response technology (IRT). After fallback, the dose will be kept stable for the rest of the Maintenance Period. Further dose changes (ie, titration) are not allowed. Subjects who are not able to tolerate the IMP during titration and after the fallback will be tapered off IMP in a blinded fashion and will be withdrawn from the study.

Maintenance Period (12 weeks)

At Visit 4 (at the end of the Stabilization Period), subjects will enter a 12-week Maintenance Period during which they will receive their target dose (or their fallback dose, if applicable). During the entire 12-week Maintenance Period, the dose of IMP (target dose or fallback dose) and concomitant AEDs must remain stable. Subjects must return to the clinic for scheduled visits as outlined in [Table 5-1](#).

Subjects who complete the Maintenance Period or who discontinue early from the study will return for an End of Treatment Visit or Early Discontinuation Visit (EDV), respectively. Subjects completing the Maintenance Period will have the opportunity to enroll into the OLE study, EP0093. They will be converted to the entry dose of the EP0093 study, 200mg bid. Subjects withdrawing from the study or deciding not to participate in the OLE study (EP0093) will be tapered off the IMP.

For subjects discontinuing the study early or not enrolling in the OLE study:

Taper Period (4 weeks)

The 4-week Taper Period will be required for subjects who choose not to enroll in the OLE study or who discontinue the study. Subjects entering the 4-week Taper Period should be gradually tapered off the IMP over a 3-week period ([Table 7-3](#)) followed by a 1-week drug-free period. A faster or slower taper schedule than the suggested 3 weeks may be implemented, if medically necessary, as per the Investigator's medical judgment. Subjects will start their taper at the EDV/End of Treatment Visit (Visit 7) and will return 1 week after last intake of IMP for the End of Taper Visit (Visit 8). Changes to concomitant AED(s) are not allowed during the taper of PSL unless they are medically necessary as per the Investigator's medical judgment to treat rebound seizures.

Safety Follow-up Period (1 month)

Safety follow up for all subjects not entering the OLE will consist of 1 required visit, 30 days after the last IMP intake (Week 23 or sooner in case of early discontinuation), including an echocardiogram. An additional follow-up echocardiogram will be performed at 6 months (± 1 month) after the last IMP intake only for subjects exposed to IMP for more than 3 weeks.

For subjects continuing to the OLE study:

Conversion Period (3 weeks)

The 3-week Conversion Period will be required for subjects who choose to enroll in the OLE study at the end of the Maintenance Period. Doses for those participating in the 3-week Conversion Period will be gradually adapted (increased or decreased) in a blinded way to reach the entry dose for the OLE. Subjects who take placebo during the Maintenance Period will receive PSL titrated to the target dose.

5.1.1 Study duration per subject

The total duration of the study per subject will be up to 27 weeks with a maximum of 19 weeks exposure to PSL. An additional follow-up echocardiogram will be performed at 6 months (± 1 month) after the last IMP intake only for subjects exposed to IMP for more than 3 weeks and either discontinuing the study or not entering the OLE.

The end of the study is defined as the date of the last SFU Visit (30 days after the last IMP intake) of the last subject in the study. Additionally, the reporting of SAEs will continue until the 6-month follow-up echocardiogram.

5.1.2 Planned number of subjects and sites

The enrollment goals are 500 subjects in the Europe/North America/Japan regions and at least 55 subjects in China at approximately 200 sites worldwide. Assuming a 20% screen failure rate, approximately 400 and at least 44 subjects will be randomized in the Europe/North America/Japan regions, and China, respectively. Because the time from protocol submission to first patient first visit (FPFV) may be longer in China, subjects enrolled in China will be in addition to the 400 subjects randomized in Europe/North America/Japan, in order to support the possibility of conducting 2 sequential analyses to maintain the blind as described in Section 13.2 and Section 13.3.1.

5.1.3 Anticipated regions and countries

The study will be conducted in Europe, North America, Japan, and China, with possible extension to other regions or countries.

5.2 Schedule of study assessments

The schedule of assessments is presented in [Table 5-1](#).

Table 5-1: Schedule of assessments

Visit	Week Number	Day Number	Visit Window (days)	Assessments	Treatment Period (16 weeks)												SFU Period (30 days after IMP intake)				
					BL Period (4 weeks)			Titration Period (3 weeks)			Stab Period (1 week)			Maintenance Period (12 weeks)						V9	Unsch Visit ^b
					V1	V2 BL	TC	V3	TC	Wk 1	Wk 2	Wk 3	TC	V4	V5	V6	V7 (EDV/EOT)	TC	V8 (Conversion)		
	Wk -4	-28				D 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16		Wk 19	Wk 20	Wk 23				
		1	7	14	21	28	56	84	112	133	140										
		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7			±7					±7		
Written informed consent	X																				
Call IRT to obtain subject number and dispensation of Subject Trial Card	X																				
Demographic data	X																				
Habits and lifestyle	X																				
Verification of inclusion/exclusion criteria	X																				
Verification of withdrawal criteria	X								X	X	X	X	X	X							
General medical/procedures history	X																				
Epilepsy history including etiology, diagnosis, surgery, and seizure history	X																				
Documentation of MRI (within 10 years)	X																				

Table 5-1: Schedule of assessments

Visit	Week Number	BL Period (4 weeks)		Treatment Period (16 weeks)									Taper/Conversion Period (3 to 4 weeks) ^a			SFU Period (30 days after IMP intake)										
		Titration Period (3 weeks)			Stab Period (1 week)			Maintenance Period (12 weeks)						V8 (Conversion)	V9	Unsch Visit ^b										
		V1	V2 BL	TC	V3	TC	Wk 1	V4	Wk 4	V5	Wk 8	V6	Wk 12				V7 (EDV/EOT)	Wk 16	TC	Wk 19	Wk 20	Wk 23				
Documentation of video-EEG ^c	X																									
AED history	X																									
Randomization (IRT)		X																								
C-SSRS Baseline ^d	X																									
C-SSRS since last visit ^{d e}		X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HADS ^d		X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SSG ^d		X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
QOLIE-31-P ^d		X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CIWA-B ^d																										
TSQM-9 ^d																										
Vital signs ^f	X	X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height ^g	X	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination ^h (XF=Full; XB=Brief)	XF	XB						XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB	XB
Neurological examination ⁱ (XF=Full; XB=Brief)	XF	XB																								

Table 5-1: Schedule of assessments

Visit	Week Number	BL Period (4 weeks)		Treatment Period (16 weeks)								Taper/Conversion Period (3 to 4 weeks) ^a			SFU Period (30 days after IMP intake)	Unsch Visit ^b			
		Titration Period (3 weeks)			Stab Period (1 week)			Maintenance Period (12 weeks)					TC	V8 (Conversion)			V8 (Taper)	V9	
		V1	V2 BL	TC	V3	TC	Wk 1	V4	Wk 4	V5	Wk 8	V6							Wk 12
Psychiatric and Mental Status		X	X			X	X	X	X	X	X	X	X	X			X		X
12-lead ECG ^j	X	X		X		X	X	X	X	X	X	X	X	X			X		X
Echocardiogram ^k	X									X									X ^l
Blood/urine sample for clinical laboratory analyses	X	X				X	X	X	X	X	X	X	X	X			X		X
Blood sample for concomitant AED assay ^{m,n}	X	X								X	X	X	X	X					
Blood sample for PSL PK analysis ^{o,n}				X			X	X	X	X	X	X	X	X					
Pregnancy test ^p	X	X		X		X	X	X	X	X	X	X	X	X			X		X
Diary dispensing (provide instructions on proper completion)	X	X		X		X	X	X	X	X	X	X	X	X			X		X
Seizure evaluation (count & type) ^q		X		X		X	X	X	X	X	X	X	X	X			X		X
Concomitant medications (AEDs and non-AEDs) and procedures	X	X		X		X	X	X	X	X	X	X	X	X			X		X
Recording of adverse events	X	X		X		X	X	X	X	X	X	X	X	X			X		X

Table 5-1: Schedule of assessments

Visit	Week Number	Treatment Period (16 weeks)										Taper/Conversion Period (3 to 4 weeks) ^a			SFU Period (30 days after IMP intake)	
		BL Period (4 weeks)			Titration Period (3 weeks)			Stab Period (1 week)			Maintenance Period (12 weeks)					
		V1	V2	TC	V3	TC	V4	TC	V5	V6	V7 (EDV/EOT)	TC	V8 (Conversion)	V8 (Taper)		V9
	Wk -4	D 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk 19	Wk 20	Wk 23				
Health-related outcomes and HRU	X	X		X		X	X	X	X		X		X			
IMP dispensing (IRT)		X		X		X	X	X	X							
IMP accountability and return ^f				X		X	X	X	X		X					
Study termination ^g											X		X			

AED=antiepileptic drug; BL=Baseline; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; EDV=Early discontinuation Visit; EEG=electroencephalogram; EOT=End of Treatment; HADS=Hospital Anxiety and Depression Scale; HRU=healthcare resource utilization; IMP=investigational medicinal product; IRT=interactive response technology; MRI=magnetic resonance imaging; OLE=open-label extension; PK=pharmacokinetic; PSL=padsevonil; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; SBP=systolic blood pressure; SFU=Safety Follow-Up; SSG=Seizure Severity Global Item; Stab=Stabilization Period; TC=telephone call; TSQM=Treatment Satisfaction Questionnaire for Medication; Unsch=unscheduled; V=visit; Wk=Week

^a Taper Period, for subjects who choose not to enter OLE study EP0093, will last for 3 weeks plus 1 week of drug-free period. Conversion Period, for subjects who choose to enter OLE study EP0093, will last for 3 weeks.

^b At any time, the subject may have an additional study visit if the Investigator or the subject and/or legal representative deem it necessary. Appropriate assessments will be conducted in relation to the reason for the visit.

^c Epileptic seizures must have been documented using video-EEG recording in the past (description or report must be available). The Investigator must consult with the UCB Study Physician or representative for confirmation of eligibility as per instructions in the Study Manual.

^d Questionnaires to be completed by all subjects prior to any other study procedures at the visit. The CIWA-B will only be completed by subjects tapering.

^e If an unscheduled visit is conducted due to safety or efficacy concerns, a C-SSRS assessment will be performed with the subject during the visit. If an unscheduled visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection, or analysis issues), a C-SSRS will not be required at these visits.

^f Vital signs measured in supine position after 5 minutes of rest include pulse rate, respiratory rate, SBP, and DBP.

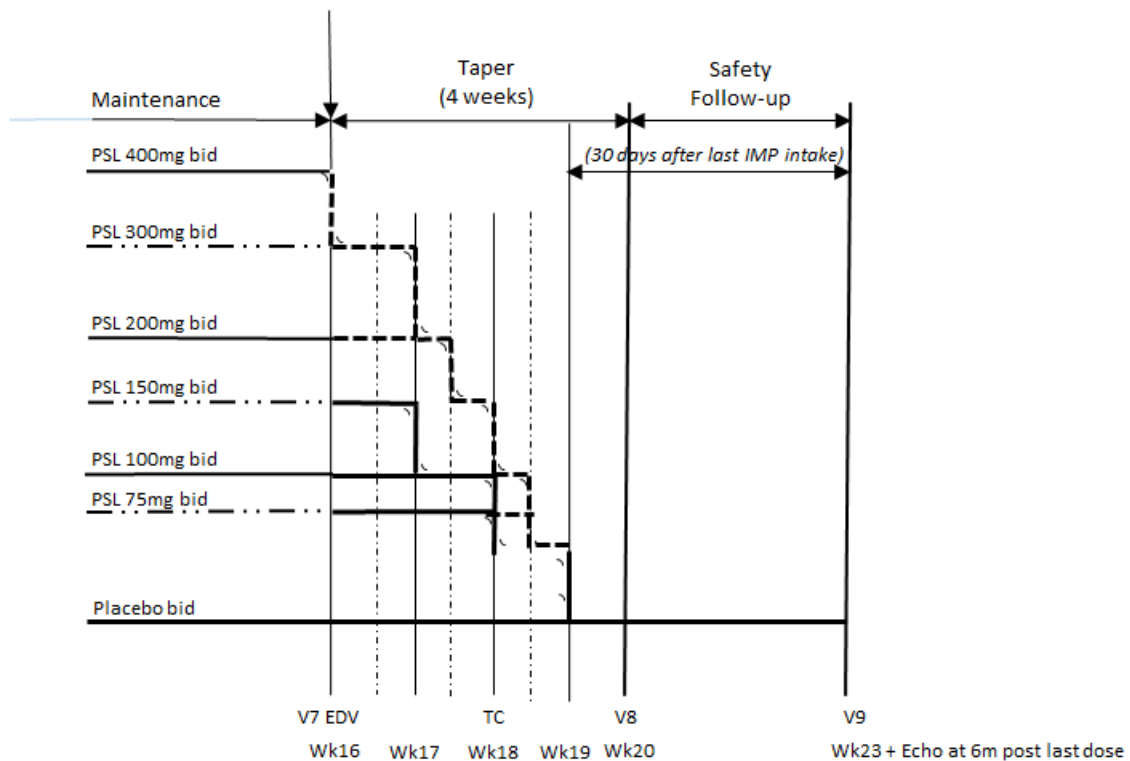
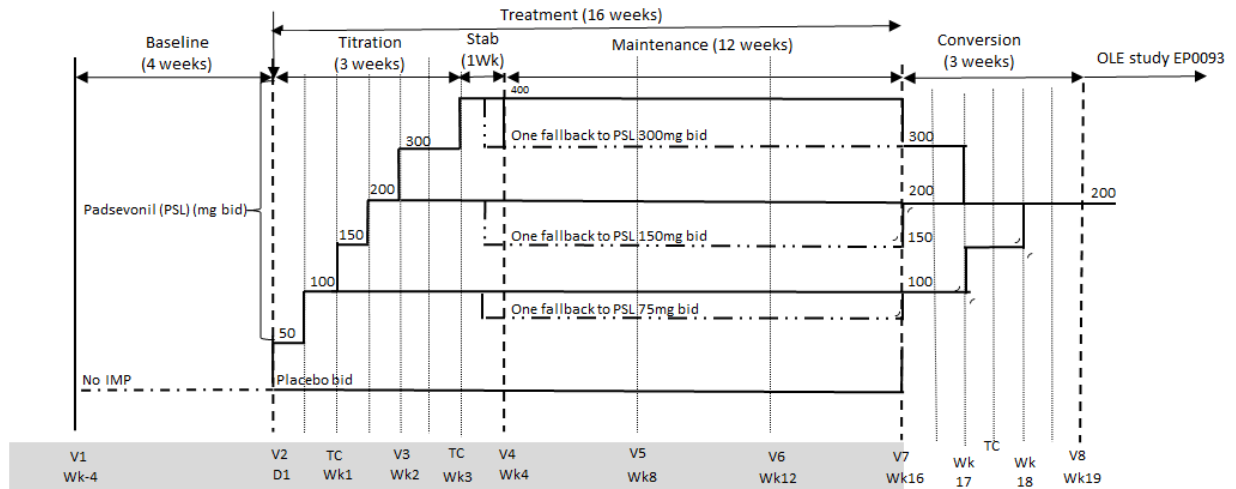
^g Height will only be measured at Visit 1.

- ^h Full physical examinations will assess cardiac and respiratory function via auscultation and review of the following body systems: general appearance; ear, nose, and throat; eyes; hair and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological; and mental status. Brief physical examinations will include a review of the following body systems: general appearance (including mental status); skin; respiratory; cardiovascular; gastrointestinal; and hepatic.
- ⁱ Brief neurological examination will include a general assessment and evaluation of reflexes, muscle strength and coordination, and cerebellar function. Full neurological examinations will include in addition, evaluation of cranial nerves, motor system (general muscle strength and tone), and sensations in upper/lower extremities.
- ^j Baseline ECG has to be scheduled and results received before Visit 2. An ECG at the SFU Visit will be performed only if abnormal at the End of Treatment or Early Discontinuation Visit. All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes.
- ^k The echocardiogram will be conducted at Visit 1. Echocardiograms will be repeated at Visit 6 for subjects continuing into the OLE study. Subjects discontinuing will have an echocardiogram 30 days after last IMP intake at the SFU Visit (except if performed at Visit 6). A repeat echocardiogram will be performed for subjects with a new finding, Grade 2 (moderate severity), or Grade 3 (severe severity).
- ^l An echocardiogram will also be performed 6 months after last IMP intake for subjects exposed to >3 weeks to IMP and discontinuing the study (but not for subjects with <3 weeks exposure).
- ^m AED samples will ideally be taken immediately prior to dose of concomitant medication on each occasion. If this is not possible, then the sample may be taken at any time after dose and the timing of sample in relation to dose should be kept the same (± 1 hour) on each occasion for each subject. Therefore, the timing of visits for each subject when AED samples are collected should be scheduled approximately at the same time whenever possible. Assay of parent PSL and metabolites may be included in the AED panel of tests at Visits 6 and 7.
- ⁿ On Visits 6 and 7, unless the concomitant AED sample is within ± 5 minutes of a scheduled MITRA[®] sample for PSL assay, a separate, additional MITRA sample will be taken at same time as the concomitant AED blood sample.
- ^o Subjects are requested to provide blood samples for measurement of PSL PK whenever possible. On Visits 3, 5, and 6, site personnel should obtain blood samples, via MITRA microsampling, for measurement of random PSL levels at any time between IMP intakes and record accurately the time of last IMP intake and the time of sample collection. On Visits 4 and 7, blood samples, via MITRA microsampling, for measurement of sparse PK profiles will be collected as follows: immediately before IMP intake (maximum 15 minute before intake) and then 3 times after (between 30 minutes and 3 hours after IMP intake), taken at least 30 minutes apart. All samples may be taken either at home or in the site or partly at home and partly at the site.
- ^p For all female subjects, serum pregnancy test at Visits 1 and 7 (in case the subject enters into the OLE study) and where applicable. Urine pregnancy test will be used at other visits for female subjects of childbearing potential.
- ^q Seizure counts are collected on the subject's daily record card on a daily basis.
- ^r At each visit following an IMP dispensation, IMP should be presented to check for compliance.
- ^s Study termination will occur at Visit 8 only for subjects enrolling in OLE study, EP0093. The SFU Visit will be performed only for subjects who do not enter the OLE study, EP0093.

5.3 Schematic diagram

A schematic diagram is provided in [Figure 5-1](#).

Figure 5-1: Study design



bid=twice daily; d=day; Echo=echocardiogram; EDV=Early Discontinuation Visit; IMP=investigational medicinal product; m=months; OLE=open-label extension; PSL=padsevonil; Stab=Stabilization Period; TC=telephone contact; V=Visit; Wk=Week

5.4 Rationale for study design and selection of dose

5.4.1 Choice of study design and endpoints

The target indication for PSL is as adjunctive therapy in the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy. The key inclusion criteria are aimed at selecting a sample of subjects from this target population. The criterion for drug resistance or failure to achieve control of seizures, with ≥ 4 tolerated and appropriately chosen past or current AEDs, is based on observations that when patients with drug-resistant epilepsy have 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 further reduced to 1% to 4% (Schiller and Najjar, 2008; Mohanraj and Brodie, 2006). Subjects also will be required to have on average at least 4 spontaneous and observable focal-onset seizures (IA1, IB, or IC) per 28 days during each 4-week interval of the 8 weeks prior to the Screening Visit and during the 4-week Baseline Period. This minimum seizure frequency was selected to provide assurance that a meaningful change in percent reduction in seizure frequency over 28 days and 50%, 75%, and 90% responder rates could be demonstrated during the 12-week Maintenance Period.

The key exclusion criteria are intended to further ensure correct diagnosis of epilepsy, that the disease is relatively stable, that there are no drugs/treatments which could confound analyses or present a safety issue as a result of DDI or efficacy against seizures, that there is no evidence of previous safety issues with other drugs that share PSL's mechanisms of action, and to mitigate risks or potential risks to subjects from this target population.

UCB regards the 12-week duration for the Maintenance Period as adequate to distinguish long-term from short-term efficacy. Moreover, 12 weeks is consistent with registration studies for recently approved AEDs as adjunctive therapy for focal-onset seizures (Moseley et al, 2016; Chung et al, 2010b; Elger et al, 2009) and conforms to the guidance documents by the FDA, Guidance for Industry, 1981 and EMA (CHMP/EWP/566/98 Rev.2/Corr, 2010). Given the increased risk of SUDEP in patients with uncontrolled seizures (Jehi, 2016) and in those randomized to placebo in clinical studies (Ryvlin et al, 2011), UCB considers that requiring patients to remain on placebo longer or for all enrolled patients to exclude dose adjustments is not acceptable. Because of the increased incidence of SUDEP, subjects should be monitored closely and, depending on the Investigator's judgment, withdrawn from the study in the event of seizure worsening, particularly subjects experiencing an increase in secondarily generalized seizures. Additionally, a 3-week Titration Period, 1-week Stabilization Period, and 12-week Maintenance Period have been assessed as adequate to evaluate the potential for the development of tolerance to BZDs associated with a reduction in long-term efficacy for both clobazam and brivaracetam.

Similarly, UCB proposes to perform an examination of the reduction in seizure frequency from Baseline to assess whether there is any evidence of a notable change in treatment effect during the course of the 16-week Treatment Period for EP0092.

5.4.2 Rationale for dose selection

Nonclinical efficacy data indicate that receptor occupancy at both the SV2 and GABA-A molecular targets contribute to the mode of action of PSL (Wood et al, 2017). In addition, a comprehensive analysis of data from 2 human PET studies (UP0036 and N01383, addressing both SV2A and GABA-A occupancy, respectively), together with population PK modelling of

patient PK data from EP0069, has allowed exploration of the occupancy levels at each of the 2 targets with simulated dosing regimens (UCB internal data). Dosing regimens of 200mg bid and 400mg bid are expected to result in high (>90%) and sustained SV2A occupancy, and quantifiable and relatively low GABA-A occupancy (ie, approximately 6% and 13% for 200mg bid and 400mg bid, respectively). These levels of target engagement are predicted by preclinical data to be required for efficacy in the drug-resistant population, and efficacy was demonstrated at 400mg bid in the clinical study, EP0069. At 100mg bid, the simulations referred to above predict sustained SV2A occupancy to be >90% in 75% of the population, and GABA-A occupancy below the limit of quantification for the flumazenil human PET model. The receptor occupancy data indicate that doses of 100, 200, and 400mg bid will engage the presynaptic SV2 proteins (for all 3 doses) and the postsynaptic GABA-A receptors (for at least the 2 higher doses). Thus, the doses of 100mg bid, 200mg bid, and 400mg bid are predicted to span the dose range which will be efficacious in the drug-resistant patient population that will enroll in EP0092 based on quantitative evidence of target coverage and systemic exposure.

Subjects completing the Maintenance Period in EP0092 will be offered the option to enter the OLE study, EP0093, with open-label treatment with PSL. This will be achieved through a Conversion Period to ensure blinding of the parent study. All subjects who choose to transition to EP0093 will enter the study after the 3-week Conversion Period at an intermediate dose of PSL 200mg bid before further individual dose adjustment can be made. This dose level was selected considering the benefit/risk balance and is based on clinical pharmacology and PET data in healthy human subjects suggesting that it will provide full occupancy at the SV2A binding site while maintaining some minimal binding to the GABA-A binding site. For subjects previously on placebo in EP0092, a full SV2A occupancy is desirable to obtain a meaningful anticonvulsive effect while minimal BZD binding will result in fewer GABA-related CNS AEs. On the other hand, for subjects exposed to high doses of PSL during the EP0092 Maintenance Period (400mg bid), the target transition dose of 200mg bid will likely maintain the full SV2A-related effect while not entirely eliminating GABA-binding related effects.

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:

General

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF is signed and dated by the subject or by the parent(s) or legal representative, where applicable. The ICF or a specific Assent form, where required, will be signed and dated according to country-specific regulations.
2. Subject/legal representative 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 is an adult (18 years of age or more).
4. Subject is of normal weight of at least 40kg (for males and females).

Epilepsy

5. Subject fulfills diagnostic criteria for epilepsy and has observable focal-onset (IA1, IB, and IC) seizures for at least 3 years at the time of enrollment (according to the ILAE Classification of Epileptic Seizures, 1981):
 - Epileptic seizures have been documented using video-EEG recordings or ictal-EEG (\pm simultaneous video) in the past (description or report is available). The Investigator must consult with the UCB Study Physician or representative for confirmation of eligibility as per instructions in the Study Manual.

If no video-EEG report is available and, in the opinion of the Investigator, epileptic seizures are definite (ie, eye-witnessed seizure report, home video documentation of habitual events, or other proof), the Investigator must consult with the UCB Study Physician or representative for a case review.
 - A brain magnetic resonance imaging (MRI) is to be performed before randomization, if no such scan was performed in the last 10 years, and a report is not available. If a scan was performed within the last 10 years but the clinical condition of the subject was progressive since the last scan, a new scan should be obtained. If MRI is contraindicated, a head computed tomography scan within the last 3 years before randomization will suffice.
6. Subject has on average ≥ 4 spontaneous and observable focal-onset seizures per 28 days (based on Investigator assessment of subject report) with at least 1 seizure during each 4-week interval of the 8 weeks prior to the Screening Visit. Additionally, subject must experience ≥ 4 spontaneous and observable focal-onset seizures per 28 days (based on Investigator assessment of subject report) during the 4-week Baseline Period.
7. Subject has failed to achieve seizure control with ≥ 4 tolerated and appropriately chosen prior AEDs, including past and ongoing treatments that were individually optimized for adequate dose and duration. Prior discontinued AED treatment would need to be assessed by the Investigator considering the patient medical records and patient and/or caregiver interview. "Prior AED" is defined as all past and ongoing AED treatments with a start date before the Screening Visit (Visit 1).

Concomitant epilepsy treatment

8. Subject is currently treated with an individually optimized and stable dose of at least 1 and up to 3 AEDs for the 8 weeks prior to the Screening Visit (Visit 1) with or without additional concurrent vagus nerve stimulation (VNS) or other neurostimulation treatments. The latter will not be counted as AEDs for the purpose of eligibility.

Laboratory parameters

9. Subject has clinical laboratory test results within the reference ranges of the laboratory or isolated test results that are outside the specified ranges and deemed as not clinically significant by the Investigator.

Birth control

10. Female subjects of child bearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1), which is confirmed to be negative by urine testing prior to the first dose of IMP at Day 1 (Visit 2) and prior to further dispensing at each study visit thereafter. Subjects will be withdrawn from the study as soon as pregnancy is known.

Female subjects will use an efficient form of contraception for the duration of the study for a period of 3 months after their last intake of IMP. Hormonal contraception may be susceptible to an interaction with the IMP, which may reduce the efficacy of the contraception method. The potential for reduced efficacy of any hormonal contraception method requires that a barrier method (preferably a male condom) also be used.

Birth control methods considered as an efficient form of contraception:

- Combined (estrogen- and progesterone-containing) hormonal contraception (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study) in combination with a barrier method (preferably a condom).
- Progesterone-only hormonal contraceptives (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study) in combination with a barrier method (preferably a condom)
- Progesterone-releasing intrauterine systems or the TCU 380A intrauterine device in combination with a barrier method (preferably a condom)
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, in combination with a barrier method (preferably a male condom)
- Male or female condom with spermicide (ie, double-barrier)
- Cap, diaphragm, or sponge with spermicide (ie, double-barrier)
- Bilateral tubal ligation
- Vasectomized partner (provided sole partner, and partner has medical proof of surgical success)
- True heterosexual sexual abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
- Women not agreeing to use birth control must be abstinent (as described in the preceding bullet) or be of nonchildbearing potential, defined as being postmenopausal (for at least 2 years before the Screening Visit [Visit 1]), verified by serum follicle stimulating hormone level >40mIU/mL at the Screening Visit (Visit 1), or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or congenitally sterile.

- Both male and female subjects must use the above-mentioned contraception during the study.
- To ensure a proper birth control, females who use hormonal contraception should use an efficient barrier contraceptive in the 3 months after their last intake of IMP.

6.2 Exclusion criteria

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

General

1. Subject has previously been randomized in this study, or a study of the medication under investigation in this study. Re-screening of a subject may be permitted but requires prior medical monitor approval, and is not permitted in case of screen failure due to seizure count.
2. Subject has participated in another study of an investigational medication (or a medical device) within the previous 30 days or 5 half-lives (whichever is longer) or is currently participating in another study of an investigational medication (or a medical device).

Laboratory parameters

3. Subject has either:
 - >2.0x upper limit of normal (ULN) of any of the following:
 - alanine aminotransferase (ALT)
 - aspartate aminotransferase (AST)
 - alkaline phosphatase (ALP)

-OR-

- >ULN total bilirubin ($\geq 1.5 \times$ ULN total bilirubin if known Gilbert's syndrome).

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 randomized 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.

If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, 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.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation before Baseline (Visit 2).

Medical conditions

4. Subject has a history or current medical condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.

5. Subject has a current psychiatric condition that occurred within the last 12 months which, in the opinion of the Investigator, could compromise the subject's safety or ability to participate in this study, including but not limited to schizophrenia, schizoaffective disorder, bipolar disorder, severe unipolar depression, dementia, or irreversible severe or progressive encephalopathy.
6. Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either question 4 or question 5 of the "Screening/Baseline" version of the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening.
7. Subject has a history of chronic alcohol or drug abuse within the last 2 years.
8. Subject has a history of cerebrovascular accident, including transient ischemic attack, in the last 6 months.
9. Subject has presence of any sign (clinical or imaging techniques) suggesting rapidly progressing (ie, not expected to stay stable during study participation) brain disorder or brain tumor. Stable lesions such as arteriovenous malformations, meningiomas, or other benign tumors are acceptable if no surgical removal is planned or likely for the duration of the study.
10. Subject has any clinical condition (eg, bone marrow depression, chronic hepatic disease, and/or severe renal impairment) that could impair reliable participation in the study or necessitate the use of medication not allowed by the protocol.
11. Subject has the presence of a terminal illness.
12. Subject has the presence of a serious infection.
13. Subject has a clinically significant abnormality on 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:
 - QT interval corrected for heart rate using Bazett's formula (QTcB) or QT interval corrected for heart rate using Fridericia's formula (QTcF) interval >450ms
 - Bundle branch blocks and other conduction abnormalities that are clinically significant according to the Investigator and/or with a PR interval ≥ 220 ms, irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats in the judgment of the Investigator, or T-wave configurations are not of sufficient quality for assessing QT interval duration
 - Subject has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
14. Subject has an abnormality on the echocardiogram at Screening (Visit 1) as assessed by the central reader that is accompanied by clinical symptoms (eg, shortness of breath, palpitations, and murmur) or a \geq Grade 2*/moderate severity abnormality or a history of rheumatic heart disease or other known valvular abnormalities (*according to the ASE Guidelines, Zoghbi et al, 2017).

Subjects whose echocardiograms are not interpretable at Screening Visit (Visit 1) by transthoracic echocardiogram (TTE), eg, due to technical difficulties or position of the heart will be excluded from the study.

Epilepsy

15. Subject has a history of or signs of generalized (formerly referred to as ‘idiopathic generalized’) or combined generalized and focal (formerly referred to as ‘symptomatic generalized’) epilepsy (Scheffer et al, 2017).
16. Subject has a history of status epilepticus within the 6-month period prior to Screening (Visit 1).
17. Subject has seizures on a regular basis that are uncountable, eg, due to clustering (ie, an episode lasting less than 30 minutes in which several seizures occur with such frequency that the initiation and completion of each individual seizure cannot be distinguished) during the 8 weeks prior to the Screening Visit and during the 4-week Baseline Period.
18. Subject has isolated auras only (ie, focal-onset seizures which involve subjective sensory or psychic phenomena only, without impairment of consciousness or awareness, [formerly referred to as simple partial seizures without an observable component]).
19. Subject has a current diagnosis of pseudo- or nonepileptic seizures, or other nonepileptic events that could be confused with epileptic seizures.
20. Subject had resective surgery for epilepsy in the last 6 months prior to study entry or plans for such a surgery within the timeframe of the study.

Epilepsy treatment

21. Subject had an epilepsy dietary therapy initiated <3 months prior to Screening (Visit 1).
22. Subject has VNS, deep brain stimulation, Responsive Neurostimulator System, or other neurostimulation for epilepsy device:
 - Implanted and activated <1 year prior to enrollment, or
 - With stimulation parameters that have been stable for <3 months, or
 - With battery life of unit not anticipated to extend for duration of study.
23. Subject is currently treated with carbamazepine, phenytoin, primidone, or phenobarbital.
24. Subject previously had serious side-effects with drugs where the side-effects were related to specific SV2A and GABA-ergic mechanisms of action.

Medical treatment

25. Subject has a known hypersensitivity to any components of PSL formulation or a history of drug or other allergy that, in the opinion of the Investigator or UCB Study Physician or delegate, contraindicates her/his participation.
26. Subject has taken or is taking any prescription, nonprescription, dietary (eg, grapefruit or passion fruit), or herbal products (eg, St. John's wort) that are strong inducers or strong

inhibitors of the cytochrome P450 (CYP)3A4 or 2C19 pathway for 2 weeks (or 5 half-lives, whichever is longer) prior to the Baseline Visit (Visit 2). Subjects taking sensitive substrates of CYP2C19 are similarly excluded. Please also note the prohibited concomitant medications (Section 7.8.2).

27. Subject has been taking vigabatrin for less than 2 years at study entry.
28. Subject has been taking vigabatrin for at least 2 years without documented normal visual fields following at least 2 years of intake.
29. Subject with a history of vigabatrin treatment who did not have a visual perimetry test at least 6 months following conclusion of treatment or the results of the visual perimetry test showed either a damage or a visual field defect associated with 1 of the following 2 conditions:
 - There was a change from a visual field test done at some point while the subject was taking vigabatrin, or
 - There was a change from a visual field test done within weeks after stopping vigabatrin administration.
30. Subject has been taking felbamate for less than 12 months and/or has no appropriate laboratory tests showing no indication of aplastic anemia or hepatic failure.
31. Subject has been taking retigabine for less than 4 years. In addition, subject is currently taking retigabine or has been exposed to retigabine with no documentation (at least every 6 months or 6 months after last exposure) of normal/stable visual acuity, slit-lamp examination, dilated fundus photography, and macular Optical Coherence Tomography imaging.
32. Subject is taking GABA-A-ergic drugs regularly (agonists [ie, barbiturates] or receptor positive allosteric modulators [ie, BZDs or non-BZDs]), excluding as needed (PRN) intake of GABA-A-ergic AEDs <3 times per week for emergencies.

Pregnancy

33. Female subject who plans to become pregnant or is breastfeeding.

6.3 Withdrawal criteria

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

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

1. Subject withdraws his/her consent.
2. The Sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
4. Subject takes prohibited concomitant medications, prescribed or over-the-counter, as defined in this protocol.
5. Subject develops an illness that would interfere with his/her continued participation.

-
6. 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.
 7. Subject with an echocardiogram showing a Grade 2 finding (moderate regurgitation/stenosis) if accompanied with moderate to severe signs/symptoms or a Grade 3 finding (severe regurgitation/stenosis) will be discontinued from the study regardless of accompanying clinical symptoms, and should begin discontinuation of the IMP. Additionally, a jump of 2 grades, from Grade 0 to Grade 2 (moderate regurgitation/stenosis) accompanied with moderate to severe symptoms or from Grade 1 to Grade 3 (severe regurgitation/stenosis) will result in subject discontinuation (see Section 6.3.2).
 8. Changes in the ECG that are regarded as clinically significant and/or that worsen over time.
 - An ECG shows an absolute value for QTcB or QTcF ≥ 500 ms or ≥ 60 ms above Baseline.
 - Subject develops second- or third-degree atrioventricular block or another clinically relevant change in ECG as determined by the Investigator.
 9. 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 IMP.

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.
 10. For subjects developing psychiatric/mood/behavioral signs or disturbances (see examples in list below) that are clinically concerning or that worsen over time, the subject should be referred immediately to a mental healthcare professional and must be withdrawn from the study.
 - Auditory or visual hallucinations
 - Delusions/paranoia/grandeur
 - Disorganized thought process
 - Agitation/aggression/apathy
 - Dysphoria/depression/mood lability/euphoria
 - Disinhibition
 - Cognitive changes/memory impairment/delirium
 - Aberrant motor behavior

11. 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 1 of the following: fever, rash, lymphadenopathy, or eosinophilia
 - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
 - Eosinophils percentage $\geq 10\%$
 - Eosinophils absolute $\geq 0.5\text{G/L}$
 - Neutrophils absolute $< 1.5\text{G/L}$
 - Platelets absolute $\leq 100\text{G/L}$
12. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

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 Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

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 be discontinued.

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

- Subjects with either of the following:
 - ALT or AST $\geq 5\text{x ULN}$
 - ALT or AST $\geq 3\text{xULN}$ and coexisting total bilirubin $\geq 2\text{xULN}$

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST $\geq 3\text{xULN}$ who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and 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 ≥ 3 xULN (and ≥ 2 x baseline) and < 5 xULN, total bilirubin < 2 xULN, and no eosinophilia (ie, $\leq 5\%$), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, and 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.

6.3.2 Echocardiogram valvular abnormalities assessments

Table 6-1 shows the grading of valvular abnormalities defined by a Grade 0 to 3 scale (according to the ASE Guidelines, 2017; Zoghbi et al, 2017) as well as the respective severity descriptions of absent, mild, moderate, and severe. Potential cardiovascular signs/symptoms that may accompany valvular abnormalities are included in the table as potential indicators of new or increasing severity of valvular changes and will be identified through routine physical examinations and AE/symptom reporting. However, symptom reporting often occurs only at an advanced stage of the disease (Iung and Vahanian, 2011), suggesting that valvular disease may or may not have accompanying clinical symptoms.

Table 6-1: Valvular abnormality grading criteria

Echocardiogram Valvular Abnormality	Severity/Description	Potential Cardiovascular Signs/Symptoms	Action
Grade 0	Absent: no regurgitation, no stenosis	None reported	None
Grade 1	Mild: trace or barely detected regurgitation/stenosis	Minimal to none	None; continued observation
Grade 2	Moderate: regurgitation/stenosis with intermediate values	Symptoms ^a : Shortness of breath on exertion or at rest; palpitation; syncope; anginal or pericarditic chest pain; fatigue or weakness	For a Grade 2/moderate severity, a decision to discontinue is based on severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this will result in subject discontinuation.
Grade 3	Severe: regurgitation/stenosis in the extreme range, often accompanied by other symptoms (eg, pulmonary congestion)	Signs: Pulmonary arterial pressure >40mm Hg and rise of >10mmHg; pulmonary edema; peripheral edema or ascites; atrial fibrillation or malignant arrhythmia; hypotension	Discontinuation of subject. For a Grade 3 of severe, subject should be discontinued regardless of accompanying clinical symptoms.
Grade increase by 2 levels	Increasing from: Grade 0 to 2 or Grade 1 to 3	Rapid onset of above signs/symptoms	A jump of 2 grades to Grade 2/moderate accompanied with moderate to severe signs/symptoms will result in subject discontinuation. A jump of 2 grades to Grade 3/severe (with/without symptoms) will result in subject discontinuation.

^a New York Heart Association Classification of symptoms; for other echocardiogram measurements, see the Echocardiogram Manual.

Echocardiograms will be obtained every 3 months and will be repeated sooner if new or worsening abnormalities are present (detailed below). Echocardiograms will be examined at the site by the local physician and then provided to the central reader where all study echocardiograms will be centrally read and interpreted. When local reads warrant, central reads will be expedited. An expedited review of an echocardiogram should be performed if the following conditions are met: (1) a Grade 2 of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms); or (3) an increase (or jump) of 2 grades (0 to 2 or 1 to 3) between echocardiograms. When any of these findings are observed, the Investigator/site should initiate an expedited review from the central reader.

Subjects with Grade 0 or 1 (absent or mild symptoms) will not undergo any additional procedures, other than continued monitoring for any symptomatic clinical events (as listed in [Table 6-1](#)).

Subjects with an echocardiogram showing a Grade 2 finding (moderate regurgitation/stenosis) will undergo a repeat echocardiogram within 1 month (unscheduled visit) to confirm the finding. For a Grade 2 echocardiogram of moderate severity, a decision to discontinue will be based on the severity of clinical signs/symptoms; if accompanied with moderate to severe signs/symptoms this would result in subject discontinuation. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms.

Subjects with an echocardiogram showing a Grade 3 finding (severe regurgitation/stenosis) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. For a Grade 3 echocardiogram with a severe severity, the subject should be discontinued from the study regardless of accompanying clinical signs/symptoms and should begin discontinuation of the IMP.

Any subject that shows an increase in 2 grades levels (Grade 0 to 2 or Grade 1 to 3) will undergo a repeat echocardiogram within 2 weeks (unscheduled visit) to confirm the finding. A jump of 2 grades to Grade 2 (moderate) accompanied with moderate to severe symptoms will result in subject discontinuation. Investigators may contact the Medical Monitor if they wish to discuss the subject's clinical signs/symptoms. If the clinical symptoms are mild, the subject is not required to discontinue. However, a jump of 2 grades, to Grade 3 (severe), will result in subject discontinuation with or without any signs/symptoms.

Regulatory authorities will be notified of any subject who is discontinued due to an abnormal echocardiogram.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

Padsevonil will be supplied by UCB as 25mg, 100mg, and 200mg film-coated tablets of different sizes and appearance. Placebo will be provided as tablets of matching size and aspect to PSL tablets allowing a double-blind packaging.

7.2 Treatments to be administered

All IMP will be administered in a double-blind manner.

All subjects will be instructed to take 5 tablets during the Titration and Taper Periods or 6 tablets during the Stabilization, Maintenance, and Conversion Periods from the appropriate medication wallets containing either PSL or placebo bid, approximately 12 hours apart. The IMP should be dosed within 30 minutes after food when practically feasible.

Subjects will be allocated to 1 of the following 4 treatment arms using the IRT system at the Baseline Visit (Visit 2):

- Padsevonil 100mg bid
- Padsevonil 200mg bid
- Padsevonil 400mg bid
- Placebo

7.2.1 Titration Period

Titration to PSL maintenance doses will occur over the course of 3 weeks as presented in [Table 7-1](#).

Table 7-1: Titration Period dosing

Dose Arm	Dose in mg per intake (morning-evening) during titration																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Week	Week 1							Week 2							Week 3								
PSL 400mg bid	50-50		100-100					150-150					200-200					300-300					
PSL 200mg bid			200-200																				
PSL 100mg bid			100-100																				
Placebo	1-1 PBO-PBO																						

bid=twice daily; PBO=placebo; PSL=padsevonil
On Day 22, the target dose will be administered.

A variation of ± 1 day is allowed for each period of 3 or 4 days and a variation of ± 3 days by week are acceptable, but the overall Titration Period variance in length should not exceed ± 1 week.

One fallback to a predefined dose based on the randomized dose will be allowed during the Stabilization Period and should occur at least 2 days prior to the start of the Maintenance Period (Visit 4) for subjects who experience tolerability issues during Week 4. The UCB Study Physician or delegate should be consulted prior to use of the fallback option and the date as well as the reason for fallback will be recorded in the source documents and in the eCRF. The dosing during the fallback option is presented in [Table 7-2](#).

Fallback may be managed via an unscheduled visit. Fallback IMP packs will be allocated via the IRT system.

Table 7-2: Dosing during fallback option

Dose arm	Fallback
PSL 400mg bid	PSL 300mg bid
PSL 200mg bid	PSL 150mg bid
PSL 100mg bid	PSL 75mg bid
Placebo	Placebo

bid=twice daily; PSL=padsevonil

After fallback, the dose will be kept stable for the duration of the Maintenance Period. Further titration is not allowed.

7.2.2 Taper Period

The Taper Period, in case of withdrawal or completion of the study, will comprise 3 weeks as presented in [Table 7-3](#). A faster or slower taper schedule than the suggested 3 weeks may be implemented if medically necessary, as per the Investigator’s medical judgment. During the Taper Period, the dose of PSL must always be administered as bid morning and evening doses, approximately 12 hours apart. Concomitant AED dosages should be kept stable throughout the entire study including the Taper Period.

Subjects should be monitored during the Taper Period for withdrawal symptoms, including behavioral changes, withdrawal-related AEs, or rebound seizures, as well as the severity of the CIWA-B withdrawal scores. Medical treatment may be required for the management of severe withdrawal symptoms. Additional AEDs (excluding prohibited medications) may be added and/or changes to dose regimens of concomitant AEDs are permitted if medically necessary as per the Investigator's medical judgment to manage rebound seizures.

Table 7-3: Taper Period dosing

Dose Arm	Dose in mg per intake (morning-evening) during taper ^a				
	Week 16	Week 17		Week 18	
PSL 400mg bid	300-300	200-200	150-150	100-100	50-50
PSL 300mg bid					
PSL 200mg bid	200-200				
PSL 150mg bid	150-150	100-100		50-50	
PSL 100mg bid	100-100				
PSL 75mg bid	75-75				
Placebo	1-1 PBO-PBO				

bid=twice daily; PBO=placebo; PSL=padsevonil

Taper steps may vary in length by ±3 days per week.

^a Taper Period for subjects who choose an early discontinuation may occur before Week 16.

7.2.3 Conversion Period

In case the subjects wish to proceed to the OLE study, the treatments and doses will be adjusted gradually in a blinded way to reach the single-entry dose into the OLE study (PSL 200mg bid) as presented in Table 7-4. During the Conversion Period, the dose of IMP must always be administered as bid morning and evening doses, approximately 12 hours apart.

Subjects taking placebo will be converted to active PSL.

Table 7-4: Conversion Period dosing

Dose Arm	Dose in mg per intake (morning-evening) during conversion		
	Week 16	Week 17	Week 18
PSL 400mg bid	300-300	200-200	
PSL 300mg bid			
PSL 200mg bid	200-200		
PSL 150mg bid			
PSL 100mg bid	100-100	150-150	200-200
PSL 75mg bid			
Placebo	50-50	100-100	150-150 ^a

bid=twice daily; OLE=open-label extension; PSL=padsevonil

Dose adjustments steps may vary in length by ±3 days per week while overall Conversion Period length should not change by more than 1 week.

^a After completion of Week 18, the dose will be 200-200, the entry dose in the OLE study, EP0093.

7.3 Packaging

Padsevonil tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations.

The IMP will be provided in blister-packed treatment cards, each providing 3, 4, or 7 days' treatment of active or placebo (plus some reserve tablets in case of unexpected event).

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for 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 IMP 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 weekly basis, including the capture of minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions 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 IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially 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 IMP until returned or destroyed.

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

The Investigator must ensure that the IMP 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, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs) or returned to UCB (or designee). 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 IMP is dispensed and at the end of the Taper/Conversion Period, subjects must return all unused IMP and empty IMP 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 and efficacy. A caregiver is allowed to help the subject with the completion of the subject diary. Subject diary completion will be reviewed at each visit.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

All subjects should continue to take their Baseline AED regimen (1 to 3 AEDs) unchanged over the whole study period. During the Taper Period, the Investigator is allowed to adjust AED dosing and/or add additional AED(s), only if medically necessary, based on his/her medical judgment.

- Drugs with possible CNS effects are allowed if at a stable dose from at least 1 month before Visit 1 and during the whole study period.
- Drugs with no CNS effects, and which are not strong CYP2C19 and/or CYP3A4 enzyme inducers/inhibitors or sensitive CYP2C19 substrates, are allowed. In cases of uncertainty, the Study Physician (or designee) should be contacted before initiating or stopping any medication during study unless it is a medical emergency.
- Vigabatrin, retigabine, and felbamate are allowed and count as add-on AEDs
 - if taken for more than 2, 4, and 1 years, respectively, and
 - if requirements mentioned in the Exclusion Criteria (Section 6.2) are met.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- GABA-A-ergic drugs: including agonists (ie, barbiturates) or receptor positive allosteric modulators (ie, BZDs or non-BZDs such as zolpidem) taken >2 times per week. Regular intake of BZDs with an indication for epileptic seizures is not allowed. However, PRN intake of GABA-A-ergic drugs <3 times per week is allowed, ie, for emergencies.
- Strong CYP3A4 inhibitors/inducers (for more details refer to Table 3-2 and Table 3-3 in FDA Drug Development Resources, Drug development and drug interactions: Table of substrates, inhibitors and inducers):
 - AEDs including carbamazepine, phenytoin, phenobarbital, and primidone.
 - Non-AED strong CYP3A4 enzyme inducers/inhibitors (ie, prescription drugs, nonprescription drugs, medical cannabis, cannabidiol, and dietary [eg, grapefruit or passion fruit]).
- CYP2C19 sensitive substrates/strong inhibitors/strong inducers including S mephenytoin, omeprazole, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampin, ritonavir (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, inhibitors and inducers).

7.8.3 Rescue medication

Benzodiazepines (as a rescue medication) are allowed for up to 2 doses within 7 days.

Each BZD PRN intake must be listed individually in the eCRF, either on the Concomitant AED Medication page or on the Concomitant non-AED Medication page, according to the indication.

7.9 Blinding

This is a double-blind study during all study periods (ie, Treatment Period [including Titration Period, Stabilization Period, and Maintenance Period] and Taper/Conversion Period). At the start of the Titration Period, subjects will be randomized to 1 of the 4 treatment arms in a 1:1:1:1 ratio (random permuted blocks).

Randomization will be stratified by current use of AEDs that bind to SV2A proteins (LEV or brivaracetam) and region (Europe, North America, Japan, and China) at the time of randomization.

If recruitment is delayed in China, 2 sequential analyses (one for subjects in Europe/North America/Japan and one for subjects in China) will be conducted as described in Section 13.2 and Section 13.3.1. In this event, at the time of the first analysis, subjects in Europe/North America/Japan will be unblinded, but subjects in China will remain blinded until all Chinese subjects have completed or terminated the study.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the IRT system. Details of the IRT system will be addressed in a separate randomization schedule specification document.

7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The Clinical Project Manager (CPM) will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the Investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at the Screening Visit (Visit 1) that serves as the subject identifier throughout the study. The subject

number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject (Visit 2), the Investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the Investigator or designee of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the eCRF.

8 STUDY PROCEDURES BY VISIT

Details of the study assessments to be performed, including whether they should be performed at specific time points prior to and after IMP administration and with respect to one another, are provided in [Table 5-1](#), and an outline of all assessments performed is provided in the sections below.

Visit windows are provided below by visit. The site should adjust the time of the visits to maintain the overall timeframe of the study or study periods.

8.1 Baseline Period (4 weeks)

8.1.1 Visit 1 (Week -4)

The following procedures will be performed:

- Obtain written informed consent
- Call IRT to obtain subject number
- Dispense Subject Trial Card
- Obtain Baseline C-SSRS data
- Collect demographic data, including habits and lifestyle
- Verify Inclusion and Exclusion criteria (laboratory parameters, ECG, echocardiogram, and MRI results may not be available at the visit but assessments need to be performed and evaluated before Visit 2)
- Collect general medical and procedure history
- Collect epilepsy history including etiology, diagnosis, surgery, and seizure history
- Brain MRI to be performed before Visit 2 if no brain MRI was performed in the past 10 years and/or no report is available. If a scan was performed within the last 10 years but the clinical condition of the subject was progressive since the last scan, a new scan should be obtained.
- Obtain the report of past video-EEG by the subject and send to UCB or delegate for review before Visit 2
- Collect AED history
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Measure body weight and height

- Perform full physical examination (refer to Section 11.7.4 for details)
- Perform full neurological examination (refer to Section 11.7.5 for details)
- Perform 12-lead ECG and have it assessed by central reader before Visit 2
- Perform echocardiogram and have it assessed by central reader before Visit 2
- Collect blood and urine samples for clinical laboratory analyses
- Collect blood sample for concomitant AED assay
- Perform serum pregnancy test (for all female subjects)
- Record concomitant medications (AEDs and non-AEDs) and procedures
- Record AEs since the signature of informed consent
- Record health-related outcomes and HRU (refer to Section 9.5 for details)
- Dispense diary and provide instructions on proper completion
- Provide appointment for next visit in 4 weeks

8.2 Treatment Period (16 weeks)

8.2.1 Titration Period (3 weeks)

8.2.1.1 Visit 2, Baseline (Day 1, 4 weeks after Visit 1, ± 3 days)

The following procedures will be performed:

- Verify Inclusion and Exclusion criteria (including results of laboratory parameters, ECG, echocardiogram, and MRI obtained since Visit 1). In the event 1 of these results is not available, the visit may be delayed by 1 week.
- Verify withdrawal criteria
- Randomize subjects using IRT
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain SSG data
- Obtain QOLIE-31-P data
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 11.7.4 for details)
- Perform brief neurological examination (refer to Section 11.7.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG

- Collect blood and urine samples for clinical laboratory analyses
- Collect blood sample for concomitant AED assay
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medications (AEDs and non-AEDs) and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 9.5 for details), with the exception of socio-professional status
- Dispense IMP using IRT

8.2.1.2 Telephone call (Week 1 ±3 days)

Subject will be interviewed to check his/her health condition including seizure experience (count and type), concomitant medications (AEDs and non-AEDs) and procedures, and AEs, as well as to verify withdrawal criteria.

8.2.1.3 Visit 3 (Week 2 ±3 days)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Obtain blood sample for measurement of random PSL levels at any time between IMP intakes and record accurately the time of last IMP intake and the time of sample collection
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medications (AEDs and non-AEDs) and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 9.5 for details), with the exception of socio-professional status
- Dispense IMP using IRT
- Check IMP accountability

8.2.2 Stabilization Period (1 week)

8.2.2.1 Telephone call (Week 3 ±3 days)

Subject will be interviewed to check his/her health condition including seizure experience (count and type), concomitant medications (AEDs and non-AEDs) and procedures, and AEs. Subject should be informed to call the Investigator within 3 days in case of AEs (in order to eventually consider fallback).

8.2.3 Maintenance Period (12 weeks)

8.2.3.1 Visit 4 (Week 4 ±7 days)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain SSG data
- Obtain QOLIE-31-P data
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 11.7.4 for details)
- Perform brief neurological examination (refer to Section 11.7.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Collect blood and urine samples for clinical laboratory analyses
- Obtain blood samples, via MITRA microsampling, immediately before IMP intake (maximum 15 minutes before IMP intake) and then 3 times after (between 30 minutes and 3 hours after IMP intake) taken at least 30 minutes apart (sparse PK profiles)
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medications (AEDs and non-AEDs) and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 9.5 for details), with the exception of socio-professional status
- Dispense IMP using IRT
- Check IMP accountability

8.2.3.2 Visit 5 (Week 8 \pm 7 days) and Visit 6 (Week 12 \pm 7 days)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Measure body weight
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG (only at Visit 5/Week 8)
- Obtain echocardiogram (only at Visit 6/Week 12) for subjects continuing into the OLE study
- Collect blood and urine samples for clinical laboratory analyses (only at Visit 6/Week 12)
- Collect blood samples for concomitant AED assay (only at Visit 6/Week 12) including an additional sample via MITRA microsampling if the AED sample is not within \pm 5 minutes of one of the scheduled PSL PK samples
- Obtain blood sample for measurement of random PSL levels at any time between IMP intakes and record accurately the time of last IMP intake and the time of sample collection
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medications (AEDs and non-AEDs) and procedures
- Record AEs
- Record health-related outcomes and HRU (refer to Section 9.5 for details), with the exception of socio-professional status
- Dispense IMP using IRT
- Check IMP accountability

8.2.3.3 Visit 7 (Week 16 \pm 7 days for EOT or earlier for EDV)

The following procedures will be performed:

- Verify withdrawal criteria
- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain SSG data
- Obtain QOLIE-31-P data
- Obtain CIWA-B data (only for subjects tapering)

-
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
 - Measure body weight
 - Perform full physical examination (refer to Section 11.7.4 for details)
 - Perform full neurological examination (refer to Section 11.7.5 for details)
 - Perform Psychiatric and Mental Status assessment
 - Obtain 12-lead ECG
 - Collect blood and urine samples for clinical laboratory analyses
 - Collect blood sample for concomitant AED assay including an additional MITRA sample if the AED sample is not within ± 5 minutes of one of the scheduled PSL PK samples
 - Obtain blood samples, via MITRA microsampling, immediately before IMP intake (maximum 15 minutes before IMP intake) and then 3 times after (between 30 minutes and 3 hours after IMP intake) taken at least 30 minutes apart (sparse PK profiles)
 - Perform urine pregnancy test (for female subjects of childbearing potential discontinuing the study only) or serum pregnancy test (for female subjects continuing into the OLE study)
 - Seizure evaluation (count and type) from subject's daily record card
 - Record concomitant medication (AEDs and non-AEDs) and procedures
 - Record AEs
 - Record health-related outcomes and HRU (refer to Section 9.5 for details)
 - Dispense IMP using IRT
 - Check IMP accountability

8.3 Taper/Conversion Period (3 to 4 weeks)

8.3.1 Telephone call (after 1 or 2 weeks in tapering/converting, as needed)

Subject will be interviewed to check his/her health condition including seizure experience (count and type), concomitant medications (AEDS and non-AEDS) and procedures, and AEs.

8.3.2 Visit 8 (end of Taper/Conversion; Week 19 ± 7 days for Conversion or Week 20 ± 7 days for Taper)

The following procedures will be performed:

- Obtain C-SSRS data since the last visit
- Obtain CIWA-B data only for subjects tapering
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Measure body weight
- Perform full physical examination (refer to Section 11.7.4 for details)

-
- Perform full neurological examination (refer to Section 11.7.5 for details)
 - Perform Psychiatric and Mental Status assessment
 - Obtain 12-lead ECG
 - Collect blood and urine samples for clinical laboratory analyses
 - Perform urine pregnancy test (female subjects of childbearing potential only)
 - Seizure evaluation (count and type) from subject's daily record card
 - Record concomitant medications (AEDs and non-AEDs) and procedures
 - Record AEs
 - Record health-related outcomes and HRU (refer to Section 9.5 for details), with the exception of socio-professional status
 - Check IMP accountability
 - Study termination (only for subjects enrolling in OLE study, EP0093)

8.4 Safety Follow-Up (Visit 9 [Week 23 or earlier for EDV, approximately 30 days after last IMP intake, ± 7 days])

The following procedures will be performed:

- Obtain C-SSRS data since the last visit
- Obtain HADS data
- Obtain SSG data
- Obtain QOLIE-31-P data
- Obtain CIWA-B data
- Measure vital signs (pulse rate, respiratory rate, SBP, and DBP), in supine position after 5 minutes of rest
- Measure body weight
- Perform brief physical examination (refer to Section 11.7.4 for details)
- Perform brief neurological examination (refer to Section 11.7.5 for details)
- Perform Psychiatric and Mental Status assessment
- Obtain 12-lead ECG
- Obtain echocardiogram for subjects discontinuing the study (except if performed at Visit 6)
- Collect blood and urine samples for clinical laboratory analyses
- Perform urine pregnancy test (female subjects of childbearing potential only)
- Seizure evaluation (count and type) from subject's daily record card
- Record concomitant medications (AEDs and non-AEDs) and procedures

- Record AEs
- Record health-related outcomes and HRU (refer to Section 9.5 for details), with the exception of socio-professional status
- End of diary recording
- Study termination, only for subjects who do not enter the OLE study, EP0093

An additional follow-up echocardiogram will be performed at 6 months (± 1 month) after the last IMP intake only for discontinued subjects exposed to IMP for more than 3 weeks and subjects not entering the OLE. **The reporting of SAEs will continue until the 6-month follow-up echocardiogram.**

8.5 Unscheduled visit/telephone call

At any time, the subject may have an unscheduled study visit/telephone call if the Investigator and/or the subject deem it necessary. An unscheduled visit may be conducted due to safety or efficacy reasons and the appropriate assessments will be conducted in relation to the reason for the visit. If an unscheduled visit is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If an unscheduled visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits (Section 11.7.6). All information, including reason for visit/telephone call, any information on AEs, etc, should be collected in the source documents and recorded in the appropriate section of the eCRF.

8.6 Open-label extension study (EP0093)

Subjects from this study have the option of taking PSL during an OLE study, EP0093. The decision to enter the OLE study must be made by the subject and/or the subject's caregiver in consultation with the Investigator. This decision must take into account the potential risks of long-term exposure to PSL and the potential benefit and risks of other treatment options available.

9 ASSESSMENT OF EFFICACY

The efficacy variables are described in detail in Section 4.1.

9.1 Seizure frequency

At the Screening Visit (Visit 1), seizure count will be based on Investigator assessment of subjects' reports during the 8 weeks prior to the Screening Visit. The subject should report on average a minimum of 4 spontaneous and observable focal-onset seizures per 28 days with at least 1 seizure during each 4-week interval of the 8 weeks prior to the Screening Visit. During the 4-week Baseline Period, the subject should experience a minimum of 4 spontaneous and observable focal-onset seizures (based on Investigator assessment of subject report). During the study, subjects will keep diaries to record daily seizure activity from the Screening Visit (Visit 1) until the end of study participation. Subjects should be reminded to bring their diaries to each clinic visit.

The written information will be discussed with the subjects at each visit in order to ensure completeness and accuracy of the diaries. As a result of the discussion, the Investigator will assess and confirm the seizures according to the ILAE codes and record the seizure types and frequency in the eCRF/diary; 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 on how 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. If the subject does not complete diary entry as per instruction, this may result in subject discontinuation from the study at any time by the Investigator or the Sponsor (Section 6.3).

The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

9.2 Seizure Severity Global Item

The SSG consists of 1 or 2 items from the Seizure Severity Questionnaire and asks the subjects to evaluate the severity of their seizures for the last 4 weeks and/or since the Baseline (in EP0092). The subjects should describe all types of seizures when answering the questions.

The SSG will be completed according to the tabular schedule of assessments (Table 5-1). At the very beginning of the visit, the SSG will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. 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 SSG will be covered in the Study Manual.

9.3 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 (Cramer and Van Hamme, 2003) is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998) that includes 31 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 according to the tabular schedule of assessments (Table 5-1). At the very beginning of the visit, the QOLIE-31-P will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. 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.

9.4 Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties both in the general population and more recently in patients with epilepsy (Lin and Pakpour, 2017; Wiglusz et al, 2016; de Oliveira et al, 2014). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating a worse state. A score below 8 is considered to be normal (Zigmond and Snaith, 1983).

The HADS will be completed according to the tabular schedule of assessments (Table 5-1). At the very beginning of the visit, the HADS will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. 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 HADS will be covered in the Study Manual.

9.5 Health-related outcomes and healthcare resource utilization

Health-related outcomes and HRU will be collected in the eCRF and/or diary during the study according to the tabular schedule of assessments (Table 5-1).

These assessments will include:

- Socio-professional status
- Healthcare provider consultations not foreseen by the protocol including the type of provider (general practitioner, specialist physician, nurse), the site of care (office-private, office-hospital, home, emergency room), and the reason leading to the consultation
- Concurrent medical procedures
- Concomitant medications
- Hospitalizations including the reason leading to the hospitalization, admission ward transfers, and length of stay
- Caregiver support needs
- Number of school or working days lost due to the medical condition of the subjects

9.6 Treatment satisfaction

The Treatment Satisfaction Questionnaire for Medication (TSQM)-9 is a 9-item questionnaire developed to provide a suitable measure of treatment satisfaction with medication (Bharmal et al, 2009). It has 5 to 7 Likert response options per item and consists of 3 subscales: effectiveness (3 items), convenience (3 items), and a global satisfaction scale (3 items). The TSQM-9 was developed from the TSQM 1.42, which has an additional subscale that measures side effects (3 items) (Atkinson et al, 2004). The estimated completion time for this questionnaire is less than 5 minutes. Scores range from 0 (worst) to 100 (best).

The TSQM-9 will be completed according to the tabular schedule of assessments (Table 5-1). At the very beginning of the visit, the TSQM-9 will be provided to all subjects. It is preferred that the subject complete the questionnaire on his/her own; however, assistance may be provided by either the study staff or caregiver if needed. 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 TSQM-9 will be covered in the Study Manual.

10 ASSESSMENT OF PHARMACOKINETIC VARIABLES

Blood samples for PK and exploratory variables will be obtained at the scheduled time points presented in [Table 5-1](#) and details of the collection, storage, preparation, and shipping of samples will be presented in a Laboratory Manual.

10.1 Pharmacokinetic variables

The PK variables for PSL and desmethyl metabolite are described in detail in [Section 4.3](#). Calculations of PK parameters will be made using population PK modeling. Additionally, plasma concentration data for concomitantly administered AEDs will be evaluated by comparing ratios of steady-state levels vs Baseline levels. For details of PK analyses, refer to [Section 13.4.2](#).

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

10.1.1 PK sampling procedures

10.1.1.1 PSL assay

Subjects are requested to provide blood samples, via MITRA microsampling, for measurement of PSL and desmethyl metabolite levels whenever possible. Site personnel are requested to discuss the importance of PK samples to measure blood levels of PSL. Site personnel should educate subjects regarding the importance of accurately recording the time of the last IMP intake and their concomitant AEDs.

On Visits 3, 5, and 6, site personnel should obtain blood samples for random PSL levels at any time between IMP intakes and record accurately the time of last IMP intake and time of the sample.

On Visits 4 and 7, blood samples for measurement of sparse PK profiles should be collected as follows: immediately before IMP intake (maximum 15 minutes before intake) and then 3 times after (between 30 minutes and 3 hours after IMP intake) taken at least 30 minutes apart.

All samples may be taken either at home or at the site when possible or partly at home and partly at the site.

10.1.1.2 Concomitant AED and exploratory pharmacokinetic evaluation

Subjects are requested to provide blood samples for a concomitant AED assay (to evaluate any DDI with PSL) at Visits 1, 2, 6, and 7.

On Visits 6 and 7, if the time point of sampling is not within 5 minutes of one of the scheduled PSL PK collections, then an additional blood sample, via MITRA microsampling, will be taken alongside (± 5 minutes) the concomitant AED sample. This process will only be done at some pre-selected sites for a limited number of subjects.

Assay of PSL metabolites may be included in the concomitant AED assay screen.

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definitions

11.1.1.1 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 ICF until the SFU Visit), 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 (ie, seizures) should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

11.1.1.2 Serious adverse event

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

- Death
- Life-threatening
(Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious
(Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.1.1.3], 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.)

11.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator’s obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 11.1.2.3.

Table 11–1: Anticipated SAEs for the epilepsy population

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

MedDRA=Medical Dictionary for Regulatory Activities, Version 19.1; SAE=serious adverse event; SOC=System Organ Class

^a Events are anticipated when occurring in the context of seizure, but not classified in MedDRA primary SOC.

11.1.1.3 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 ≥ 3 xULN ALT or AST with coexisting ≥ 2 xULN total bilirubin in the absence of ≥ 2 xULN 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.

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.

11.1.2.1 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.

11.1.2.2 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

11.1.2.3 Additional 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 SAE 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 SAE Report form will be provided to the Investigator. The 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 to UCB 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 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 6 months from the last IMP intake for each subject (ie, until the 6-month follow-up echocardiogram), and to also inform 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 IB.

11.1.3 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. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 11.6.1.4.

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, 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 IMP.

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

11.2 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 PS department by providing the completed Pregnancy Report and Outcome form (for contact details see SAE 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 EDV.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the EDV.
- An SFU Visit should be scheduled 1 week after the subject has discontinued her IMP.

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 IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization (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 SAE 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 SAE Report form.

11.3 Suspected transmission of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

11.4 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in 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).

11.5 Safety signal detection

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

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory, or ECG results) for which data will be periodically reviewed during the course of the study.

In addition, an unblinded independent DMC (Section 13.7) will oversee safety data approximately every 6 months (subject to DMC recommendation) during the course of the study during which the safety of PSL will be assessed. The safety variables and the decision rules to be used will be specified in the DMC Charter. This analysis will inform any decisions regarding changes in study conduct and/or study termination. The precise membership, scope, and responsibilities of the DMC will be described in the DMC Charter.

11.6 Laboratory measurements

Laboratory assessments will be conducted using standard methods at a central laboratory. The central laboratory will provide the Investigator with dedicated, standardized sampling equipment (labels, needles, tubes), and a study-specific Laboratory Manual, which will explain how to use the equipment and how to ship the samples to the central laboratory. The laboratory parameters measured are presented in [Table 11–2](#).

The total blood volume drawn for clinical laboratory assessments per subject will be a maximum of 12.1mL by sampling, which includes 2mL for hematology, 5mL for blood chemistry, 5mL for AED plasma level (including back-up samples for AED assay), 20µL for PSL plasma level, and 80µL for PK measurements.

Table 11–2: Laboratory measurements

Hematology	Chemistry	Urinalysis
Basophils	ALP	Glucose
Eosinophils	ALT	pH
Hematocrit	AST	RBC
Hemoglobin	Bilirubin	Total protein
Lymphocytes	BUN or urea	WBC
MCH	Calcium	Microscopy (WBC, RBC, casts, crystals, bacteria) ^a
MCHC	Chloride	Other
MCV	Creatinine	FSH
Monocytes	Glucose	
Neutrophils	HDL	
Platelet count	LDH	
RBC count	LDL	
WBC count	Magnesium	
	Potassium	
	Sodium	
	Total bilirubin	
	Total cholesterol	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; HDL=high density lipoprotein; LDH=lactate dehydrogenase; LDL=low density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

^a Microscopy will be performed only in case of abnormalities.

Where applicable (ie, for women of childbearing potential), a serum pregnancy test (β -human chorionic gonadotropin levels) will be conducted at Visits 1 and 7 only. A urine pregnancy test will be used at other visits. If pregnancy is suspected at any time during the study, an interim test should be performed.

Women not agreeing to use birth control must be abstinent or be of nonchildbearing potential, defined as being postmenopausal (for at least 2 years before the Screening Visit [Visit 1]), verified by serum follicle stimulating hormone level >40mIU/mL at the Screening Visit (Visit 1), permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or congenitally sterile (see also Section 6.1).

Sampling time and last AED intake should be recorded in the eCRF.

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 AEs 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 11.1.1.3), and, if applicable, also reported as an SAE (see Section 11.1.1.2).

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 approach to investigate PDILI is summarized in Table 11-3.

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		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN	NA	Yes				
≥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 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

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 $\geq 2 \times$ ULN 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 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 Section 11.6.1.3) 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

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, ie, drug-induced liver injury is excluded, 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 $\geq 3xULN$.
- Subject's total bilirubin is $<1.5xULN$.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. 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 and understands their individual benefit/risk for restarting IMP and this is adequately documented.

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 $\geq 1.5 \times \text{ULN}$, 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

^a Measured only for subjects with ALT $> 8 \times \text{ULN}$, 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: <ul style="list-style-type: none"> • 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 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

Other safety measurements will include vital signs measurement, 12-lead ECGs, echocardiograms, physical examination, neurological examination, assessment of suicidality, and Psychiatric and Mental Status. These will be conducted at the time points shown in [Table 5-1](#).

11.7.1 Vital signs measurement

Vital signs will be measured at the scheduled time points presented in [Table 5-1](#).

Vital signs including pulse rate, respiratory rate, SBP, and DBP 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 Electrocardiograms

The 12-lead ECG recordings will be measured by a qualified technician at the scheduled time points presented in [Table 5-1](#).

All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes. Each 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 determine if there are any abnormalities that are considered clinically significant for a particular subject. Electrocardiograms will also be sent to a specified central reader for review as detailed in the ECG Manual. The following ECG parameters will be recorded: heart rate, PR interval, QRS duration, QT interval, QTcB or QTcF, and Investigator's conclusion on ECG profile.

11.7.3 Echocardiograms

Echocardiograms will be performed at the scheduled time points presented in [Table 5-1](#). An echocardiogram will be performed at Visit 6 if the subject is continuing in the OLE study. All subjects discontinuing the study will have an echocardiogram performed 30 days (± 1 week) after the last IMP intake except for subjects who have had an echocardiogram performed at Visit 6. For subjects discontinuing with more than 3 weeks exposure to IMP or for subjects not entering the OLE study, an echocardiogram will be performed at 6 months (± 1 month) after the last IMP intake.

Two-dimensional Doppler echocardiography will include the following measurements/observations:

- Epicardial abnormalities
 - Functional measurements
 - Diastology (ie, Mitral Valve E/A waves, etc.)
 - Systolic (ie, Left Ventricular Ejection Fraction, LVEF, etc.)
- Epicardial effusion
 - Amount of effusion
 - Pericardial thickness
- Valvular abnormalities
 - Measurement of valve regurgitation/stenosis
 - Measurement of left atrial volume

Subjects whose echocardiograms are not interpretable by TTE at study entry, eg, due to technical difficulties or position of the heart, will not be randomized. In the event echocardiograms are not interpretable by TTE during the study, alternative assessments should be done using either transthoracic echocardiography or cardiac MRI in these particular instances.

Echocardiograms should be acquired by a qualified technician. The echocardiograms will be examined by the local physician. Echocardiograms will also be sent to a central cardiologist for review as detailed in the Echocardiogram Manual.

A repeat echocardiogram will be performed for subjects with a new finding of Grade 2 (moderate severity) or Grade 3 (severe severity) (see Section 6.3.2).

Subjects with an echocardiogram showing an abnormality meeting the withdrawal criteria (see Section 6.3) are to be discontinued from the study. An expedited review of an echocardiogram (at the central reader) should be requested if the following conditions are met: (1) a Grade 2 of moderate severity, accompanied by moderate or severe signs/symptoms; (2) a Grade 3 finding of severe severity (with or without accompanying symptoms); or (3) an increase (or jump) in 2 grades (0 to 2 or 1 to 3) between echocardiograms. When any of these conditions are met, the Investigator/site should initiate an expedited review from the central reader (see Echocardiography Manual). Regulatory authorities will be notified of any discontinuations.

In case of discontinuation, the subject should return for an EDV and SFU Visit (Visit 9) including an echocardiogram within approximately 1 month after last IMP intake and if taking IMP greater than 3 weeks, should also return for a 6-month echocardiogram. The corresponding TEAEs should be followed up until they have resolved, have a stable sequelae, or the subject is lost to follow-up.

11.7.4 Physical examination

Physical examinations will be performed at the scheduled time points presented in Table 5-1. Findings that are considered clinically significant changes since the physical examination at the Baseline Visit will be recorded as AEs.

A full physical examination will include cardiac and respiratory function via auscultation and review of the following body systems: general appearance; ear, nose, and throat; eyes; hair and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological; and mental status.

A brief physical examination will include review of the following body systems: general appearance including mental status; skin; respiratory; cardiovascular; gastrointestinal; and hepatic.

In addition, height will be measured at the Screening Visit (Visit 1) with the subject not wearing shoes and the outcome will be rounded to the nearest 0.5cm. Body weight will be measured at the scheduled time points presented in Table 5-1. 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.

11.7.5 Neurological examination

Neurological examinations will be performed at the scheduled time points presented in [Table 5-1](#). Findings that are considered clinically significant changes since the neurological examination at the Baseline Visit will be recorded as AEs.

A full neurological examination will include: general assessment; evaluation of reflexes, muscle strength and coordination, and cerebellar function; evaluation of cranial nerves and motor system (general – muscle strength and tone); and sensations in upper/lower extremities.

A brief neurological examination will include: general assessment and the evaluation of reflexes, muscle strength and coordination, and cerebellar function.

11.7.6 Assessment of suicidality

The C-SSRS will be completed at the scheduled time points presented in [Table 5-1](#).

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The Investigator's decision about patient continuation in the study or patient withdrawal from the study if the patient has a positive response to the C-SSRS question 4 should be based on the benefit/risk balance for continuation or discontinuation of study treatment in view of the individual patient circumstances, condition, attained efficacy, causality, alternative risk management options, etc.

If an additional visit (or unscheduled visit) is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If an additional visit (or unscheduled visit) is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

Details of the case must be documented by the Investigator (PI or Investigator physician, not site staff conducting the C-SSRS) and provided to UCB via the SAE reporting process.

11.7.7 Psychiatric and mental status

The psychiatric and mental status of subjects will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. The Psychiatric and Mental Status assessment will be performed at Baseline and all scheduled visits ([Table 5-1](#)). The parameters that will be evaluated are orientation, attention, memory, mood, calculus, behavior, and thinking or feeling. These parameters will be assessed as normal or abnormal and then determined whether clinically significant. In addition, if present and abnormal, psychiatric symptoms, mental impairment, and behavioral problems will be assessed as to whether they are clinically significant.

11.7.8 Withdrawal monitoring

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire at the scheduled time points presented in [Table 5-1](#). The CIWA-B questionnaire contains 22 questions which are selected to distinguish withdrawal symptoms from other symptoms (Busto et al, 1989).

Subjects should be monitored during the Taper Period for withdrawal symptoms, including withdrawal-related AEs or seizures as well as the severity of the CIWA-B withdrawal scores. Withdrawal symptoms may require medical treatment for management of severe withdrawal symptoms.

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

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a subject from immediate hazard before notifying UCB (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

After implementation of such a measure, the Investigator must notify the CPM of the Sponsor within 24 hours and follow any local regulatory requirements.

12.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring 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 UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each subject). Monitoring visits will provide UCB (or designee) 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, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

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

- Demographic data
- Childbearing potential and birth control
- Vital signs
- Body weight and height
- Physical and neurological examinations
- Healthcare provider consultation not foreseen by the protocol
- Caregiver use
- Socio-professional data
- Number of school/working days lost

Diaries will be transcribed into the eCRF and will be considered as source documentation.

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 each printout and the data stored in the computer to ensure all data are consistent.

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

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

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. A risk-based approach will be used to monitor the data from the site including tools such as source data verification and remote data review. These processes will be described in the Study Manual.

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 an 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) must 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 eCRFs 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 or electronically loaded into the system. 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, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused 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 subjects 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, 2016 [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 IRB/IEC SOPs, ICH-GCP, and applicable regulatory requirements.

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

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

Analysis sets are defined in the following sub-sections.

13.1.1 Enrolled Set

The Enrolled Set (ES) consists of all subjects who have given informed consent.

13.1.2 Randomized Set

The Randomized Set (RS) consists of all subjects randomized into the study.

13.1.3 Safety Set

The Safety Set (SS) consists of all subjects who were administered at least 1 dose or a partial dose of IMP. The SS will be used to summarize and analyze all safety variables. In case of a dosing administration error, summaries and analyses using the SS will be conducted according to actual treatment received.

13.1.4 Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects in the RS who were administered at least 1 dose or a partial dose of IMP and have seizure frequency data at Baseline and at least 1 post-Baseline time point during the Treatment Period. In case of a dosing administration error, or change in treatment dose, summaries and analyses using the FAS will be conducted according to randomized treatment. The FAS will be the primary analysis set for all efficacy summaries and analyses.

13.1.5 Per-Protocol Set

The Per-Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had at least 1 post-Baseline efficacy measurement and who had no major protocol deviation affecting the primary efficacy variable, as confirmed during a pre-analysis data review meeting, conducted prior to study unblinding.

13.1.6 Pharmacokinetic Set

The PK Set is defined as a subset of the FAS, consisting of those subjects who provide at least 1 PSL concentration measure.

13.2 General statistical considerations

With enrollment goals of 500 subjects in the Europe/North America/Japan regions and at least 55 subjects in China, and assuming a 20% screen failure rate, approximately 400 and at least 44 subjects will be randomized in the Europe/North America/Japan regions, and China, respectively. In the event that China and Europe/North America/Japan meet these randomization targets at approximately the same time, a single analysis will be conducted after all subjects have completed or terminated the study to support submission to the European, North American, Japanese, and Chinese regulatory agencies. However, because the time from protocol submission to PPFV may be longer in China, subjects enrolled in China will be in addition to the 400 subjects randomized in Europe/North America/Japan.

If recruitment is delayed in China, enrollment will be stopped in Europe/North America/Japan regions after approximately 400 subjects have been randomized in these regions, while enrollment will continue in China until at least 44 subjects have been randomized. In this event, subjects in China will not be part of the first analysis and 2 sequential analyses will be conducted as described in Section 13.3.1 in order to maintain the blind.

Summary statistics will be provided for all efficacy, safety, and Baseline/demographic variables. Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard

deviation [SD], standard error, minimum, maximum, 25th and 75th percentiles) will be tabulated. Unless otherwise mentioned, statistical hypothesis tests will be 2-sided at the 5% significance level.

The SAP will describe additional features and detailed methodology as well as handling of missing data.

13.3 Planned efficacy/outcome analyses

The efficacy variables will be analyzed as described below using the FAS.

Total seizure frequency per 28 days will be derived from the seizure count information recorded on the diary card and is defined as the number of seizures standardized to a 28-day period. It is computed as the number of seizures recorded over a period, divided by the total number of days in that period, multiplied by 28. Observable focal-onset seizures refers to Type IA1, IB, and IC seizures (according to the ILAE Classification of Epileptic Seizures, 1981). Focal-onset seizures include all Type I seizures. Seizure-free status and seizure-free days include all (Type I, II, and III) seizure types.

13.3.1 Analysis of the primary efficacy variable

All analyses of the primary efficacy variable will be repeated on the PPS.

In the event that enrollment is completed in China and Europe/North America/Japan at approximately the same time, a single analysis will be conducted including all randomized subjects. If the enrollment period in China is extended to attain the target of at least 44 subjects randomized in that country, then 2 analyses will be carried out in a sequential fashion with statistical significance required from the first analysis in order for the second analysis to take place. For analyses to support European/North American/Japanese regulatory submissions, the primary analysis will be carried out with a significance level of 0.05 when all randomized (approximately 400) non-Chinese subjects have completed or terminated the study. If the first analysis reaches statistical significance, a subsequent analysis will be carried out for all randomized (approximately 444) subjects (at the 0.05 significance level) to support the submission for China. If the first analysis does not reach statistical significance, no further testing will be done, for either the European/North American/Japanese regulatory submissions or for the Chinese submission.

13.3.1.1 Analysis of the primary efficacy variable for the US FDA, PMDA, Chinese FDA, and other regulatory authorities not specified in Section 4.1.1.2

Pairwise comparisons of 400mg bid, 200mg bid, and 100mg bid dose groups versus placebo will be carried out using the following analysis model. Type 1 error will be controlled by the Hochberg step-up procedure within SAS[®] Proc Multtest.

For the US FDA, PMDA, Chinese FDA, and other regulatory authorities not specified in Section 4.1.1.2, the primary efficacy variable is the change in log-transformed observable focal-onset seizure frequency from Baseline, over the 12-week Maintenance Period. The 28-day Baseline and post-Baseline (maintenance) seizure frequency will be transformed with the natural logarithm, specifically $\ln(x+1)$, where x represents the 28-day seizure frequency. The transformed seizure frequency data will be analyzed using analysis of covariance (ANCOVA)

with treatment group as the main factor, Baseline log-adjusted seizure frequency as a continuous covariate, and Baseline SV2A and region used as a categorical factors. Pairwise contrasts will be constructed to compute estimated effects of each dose from placebo.

All pairwise analyses of the primary efficacy variable will be repeated on the PPS.

If the second analysis is performed for Chinese FDA (Section 13.3.1), a dose will be concluded statistically significant in the second analysis only if the dose is statistically significant in the first and second analyses.

13.3.1.2 Analysis of the primary efficacy variable for EMA and regulatory authorities who reference EMA

For EMA and regulatory authorities who reference EMA, the primary efficacy variable will be the 75% responder rate in observable focal-onset seizures during the Maintenance Period and will be analyzed using logistic regression with factors for treatment group, Baseline seizure frequency, and Baseline SV2A use. If there are issues with convergence, Baseline SV2A use and region will be dropped.

The same methodology carried out in Section 13.3.1.1 for US FDA, PMDA, Chinese FDA, and other regulatory authorities will be applied to the pairwise analyses.

13.3.2 Secondary efficacy analysis

13.3.2.1 Secondary efficacy variables for the US FDA, PMDA, Chinese FDA, and other regulatory authorities not specified in Section 4.1.1.2

The 75% responder rate in observable focal-onset seizures during the Maintenance Period is a secondary efficacy variable for the FDA. It is the primary efficacy variable for EMA. The analyses are described in Section 13.3.1.2.

In addition, the 50% responder rate in observable focal-onset seizures during the Maintenance Period will be analyzed using logistic regression as described in Section 13.3.1.2.

Analyses of the percent change in seizure reduction endpoints will be performed using the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator will be used to estimate the median percent reduction in seizures between groups and its corresponding 95% CI will be provided.

13.3.2.2 Secondary efficacy variables for EMA and regulatory authorities who reference EMA

The change in log-transformed observable focal-onset seizure frequency from Baseline over the 12-week Maintenance Period is a secondary efficacy variable for EMA. It is the primary efficacy variable for the FDA. The analyses are described in Section 13.3.1.1.

In addition, the 50% responder rate in observable focal-onset seizures during the Maintenance Period will be analyzed using logistic regression as described in Section 13.3.1.2.

Analyses of the percent change in seizure reduction endpoints will be performed using the Wilcoxon-Mann-Whitney test. The Hodges-Lehmann nonparametric estimator will be used to estimate the median percent reduction in seizures between groups and its corresponding 95% CI will be provided.

13.3.3 Other efficacy analyses (this applies for all regulatory authorities)

All other analyses of the 75% and 50% responder rate endpoints will be analyzed using the same logistic regression model as specified in Section 13.3.1.2. Analyses of 90% responder rate and seizure freedom will use the same methodology. In addition to observable focal-onset seizures and focal-onset seizures, analyses will also be carried out on all seizures (seizure-free status and seizure-free days) during the 12-week Maintenance Period and the 16-week Treatment Period.

All other analyses of the change from Baseline in seizure frequency will be analyzed using the ANCOVA model on the log-transformed data, as specified in Section 13.3.1.1.

The time-to-return to Baseline observable focal-onset seizure frequency will be analyzed using Kaplan-Meier methodology. Additional details of the analysis will be captured in the SAP.

The QOLIE-31-P and SSG assessments will be summarized using descriptive statistics by each available visit.

13.4 Planned safety and other analyses

13.4.1 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]). Adverse events will be summarized by MedDRA System Organ Class and Preferred Term. The incidence of SAEs, AEs leading to premature discontinuation or dose tapering, and related AEs, and the incidence of AEs by maximum intensity, will also be summarized.

Laboratory values, ECG data (heart rate, PR interval, QRS duration, QT interval, QTcB or QTcF, and Investigator's conclusion on ECG profile) and arrhythmias, vital signs, weight, and changes from Baseline in these measures will be summarized by period, visit, and treatment group. Possibly clinically significant treatment-emergent abnormalities for laboratory values, vital signs, and weight will be listed and summarized by period and visit for each treatment group.

Electrocardiogram abnormalities as well as physical and neurological abnormalities will also be listed by period and visit. Quantitative safety parameters will be summarized descriptively by time point and treatment group. Categorical safety summaries will provide the number and percentage of subjects within each summarized category.

Doppler echocardiogram results at Baseline and during and after treatment, and changes from Baseline, will be listed and descriptively summarized.

All C-SSRS data obtained at Baseline and subsequent visits will be reported as a listing ordered by subject and visit. Psychiatric and Mental Status assessment and CIWA-B data will also be included using listings.

13.4.2 Pharmacokinetic analyses

Blood concentrations of PSL will be determined from blood samples obtained in the study, during the Titration and Maintenance Periods in order to investigate the PK of PSL.

The PK parameters calculated include, $AUC_{(0-\tau)}$, AUC , C_{max} , t_{max} , $t_{1/2}$, C_{trough} , and $C_{max ss}$.

The PK variables will be derived from population PK modeling.

The PK parameters of PSL will be listed and summarized using the following descriptive statistics: number of observations, geometric mean, lower and upper 95% CI, geometric coefficient of variation, arithmetic mean, SD, median, and minimum and maximum values. Graphical outputs over time will be produced on the trough plasma PSL concentrations.

Plasma concentration data for concomitantly administered AEDs will be assessed by evaluating ratios of steady-state levels while on maintenance PSL vs Baseline (pre-PSL) levels.

An exploratory comparison of PSL blood levels derived from the MITRA sampler with conventional venous sampling may be made.

An exploratory evaluation of the PSL desmethyl metabolite may be undertaken.

13.5 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, define the PPS, and 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.

13.6 Handling of dropouts or missing data

Seizure frequency will be computed over non-missing diary days. Unless noted otherwise, for subjects who prematurely discontinued the study, the last observation carried forward method will be applied to obtain a seizure frequency estimate for the Maintenance Period:

- Subjects discontinued during the Titration and Stabilization Periods: seizure frequency will be calculated using all available data in the Titration and Stabilization Periods and carried forward for the Maintenance Period.
- Subjects discontinued during the Maintenance Period: seizure frequency will be calculated using all available data in the Maintenance Period.

Additional details and sensitivity analyses for missing data will be described in the SAP.

13.7 Data monitoring

An independent DMC has been formed for EP0091 and EP0093; the same DMC will monitor the ongoing safety of this study. The DMC consists of at least 3 individuals. Voting members of the DMC include external physicians with experience in treating drug-resistant epilepsy and a cardiologist. Additionally, at least 1 member may be a statistician. All members have experience and expertise in clinical studies. The DMC members may not participate in the study as principal or co-Investigators, or as subject care physicians. The DMC will regularly review study data and evaluate the treatments for excess adverse effects and other potential safety issues. The DMC may provide recommendations to the Sponsor concerning continuation, termination, or other modifications of the study based on the observed adverse effects of the treatment under investigation. Such recommendations may include stopping enrollment into a PSL dose arm for

safety and tolerability reasons and allocating remaining patients to remaining PSL dose or placebo arms. Study enrollment will not be halted during DMC review of the safety data. The DMC may also be asked to provide a review of final study results, as deemed appropriate. The detailed role, scope, composition, responsibilities, and operation of the DMC, as well as the identity of the DMC members, will be defined in a separate DMC Charter.

Safety and tolerability data will be made available to the DMC at each meeting as described in the DMC Charter. The data will be provided in a semi-unblinded fashion (data will be visualized by real treatment groups, but the treatment/dose assigned to each group will remain blinded) and the full unblinding can be requested by the DMC members, if appropriate. Pharmacokinetic data may be provided to the DMC at their request. These safety, tolerability, and PK data will be presented by individuals not otherwise involved in the conduct of the study. The deliberations and decisions of the DMC will be formally documented.

Ad hoc DMC meetings can be held for other reasons if deemed appropriate by the Sponsor or the DMC members.

In addition to ongoing review of safety data and safety signal detection within UCB, the occurrence of AEs of interest including cardiac and behavioral AEs, in particular, will be monitored by the DMC to provide an assessment of the risk of occurrence of these events in the study.

The DMC procedures will ensure that the data remain blinded to the study team and Investigators at all times throughout the conduct of the study until the data have been unblinded. Only DMC members and an independent statistical group will have access to unblinded safety data emerging from the study. DMC members will also have access to unblinded efficacy data when required. It is understood that maintaining validity and integrity of the study is of paramount importance to ensure its acceptability to the Sponsor, the scientific community, and health authorities.

13.8 Determination of sample size

In the event that 2 data analyses are conducted to accommodate an extended enrollment period in China, the initial data cut and analysis will be performed after all randomized non-Chinese subjects (approximately 400) have completed or terminated the study. The safety and efficacy analyses from this first data cut will serve as the basis for the European, North American, and Japanese submissions for marketing authorization. The power for this analysis is greater than 90%, at the 2-sided 5% significance level. Because of uncertainty regarding the time point when China will join the global program and the duration of recruitment in China, a second efficacy and safety analysis for all randomized subjects (approximately 444) will also be performed: the power in this case remains greater than 90%, at the 2-sided 5% significance level. The safety and efficacy analyses from the second data cut will serve as the basis for submission for marketing authorization only for China.

Kawai (Kawai et al, 2008) showed the recommended proportion of subjects from subgroups needed in order to have a high probability of being able to generalize study results across subgroups. With at least 10% of subjects in the Chinese subgroup ($n \geq 44$) there is a high probability (>0.8) that study results will be similar across subgroups in the study.

The sample size was calculated based on achieving 90% power to observe a statistically significant result for either the 400mg bid and 200mg bid or 200mg bid and 100mg bid doses when compared to PBO for both the primary variable for FDA/PMDA/CFDA, change from Baseline of the log transformed ($\ln x+1$) 28-day adjusted seizure frequency, and the primary variable for EMA, the 75% responder rate. The log reduction from Baseline in seizure frequency was assumed to be 0.195 for PBO and 0.670, 0.754, and 0.780 for 100mg bid, 200mg bid, and 400mg bid doses of PSL, respectively. A common SD of 0.985 was assumed. For the 75% responder rate endpoint, assumptions were a 0.121 responder rate for PBO and corresponding responder rates of 0.301, 0.332, and 0.342 for the 100mg bid, 200mg bid, and 400mg bid doses of PSL, respectively. These estimates are based on prior experience in epilepsy together with the EP0069 study results. A significance level of 0.05 was chosen, and a 2-sided test assumed. With power of greater than 90%, a 2-sided Type-1 error of 5%, and all dose groups of the same size, 100 subjects are required per arm, giving a total of 400 subjects. An additional group of at least 44 subjects will be included from China. Assuming a screening failure rate of approximately 20%, it is anticipated to enroll approximately 555 subjects (approximately 500 in Europe, North America, and Japan, and at least 55 in China) and randomize approximately 444 subjects (approximately 400 in Europe, North America, and Japan, and at least 44 in China) in the 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 ICF 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 ICF. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF 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 ICF by the IRB/IEC and use of the amended form.

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

The subject may withdraw 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 ICF. 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 or legal representative 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 Institutional Review Boards and Independent Ethics Committees

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

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

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

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

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

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

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

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 assigned at Screening.

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

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 IRB/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.

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17 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

I will ensure that all 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

18 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: ep0092-protocol
Version: 1.0
Document Number: CLIN-000122004
Title: EP0092 Study Protocol
Approved Date: 28 Sep 2018

Document Approvals	
Approval Verdict: Approved	Name: Tony Daniels Capacity: Clinical Date of Signature: 27-Sep-2018 21:04:07 GMT+0000
Approval Verdict: Approved	Name: Konrad J. Werhahn Capacity: Clinical Date of Signature: 28-Sep-2018 06:47:51 GMT+0000
Approval Verdict: Approved	Name: Jon Cooke Capacity: Clinical Date of Signature: 28-Sep-2018 09:52:43 GMT+0000