PROTOCOL UP0070

A MULTICENTER, OPEN-LABEL, PARALLEL-GROUP STUDY IN STUDY PARTICIPANTS WITH EPILEPSY TO EVALUATE THE EFFECT OF OXCARBAZEPINE ON THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF PADSEVONIL

PHASE 1

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SERIOUS ADVERSE EVENT REPORTING

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AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
bid	twice daily
BMI	body mass index
BP	blood pressure
BRV	brivaracetam
BZD	benzodiazepine
cBZR	central benzodiazepine receptor
CDMS	clinical data management system
CI	confidence interval
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report form
EOS	End of Study
EPM	Exploratory Project Manager
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
$GABA_A$	gamma-aminobutyric acid type A
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV-1/2Ab	human immunodeficiency virus-1/2 antibody
HLA	human leukocyte antigen
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
IPD	important protocol deviation
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LEV	levetiracetam
LTG	lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities
MHD	Mono Hydroxy Derivate
NCA	noncompartmental analysis
OTC	over the counter
OXC	oxcarbazepine
PD	pharmacodynamics(s)
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PR	pulse rate
PS	Patient Safety
PSL	Padsevonil
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	respiratory rate

SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-Up
SOC	System Organ Class
SOP	Standard Operating Procedure
SV2	synaptic vesicle protein 2
ULN	upper limit of normal

1 SUMMARY

Padsevonil (PSL; previously known as UCB0942) is a novel chemical entity with selective dual synaptic vesicle protein 2 (SV2) and central benzodiazepine receptor (cBZR) site affinity. It is currently being investigated for the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy.

Many antiepileptic drugs (AEDs) are associated with drug-drug interactions. Preclinical data indicate that PSL metabolism is mediated mainly by cytochrome P450 (CYP)3A4 with minor involvement of CYP2C19. Consequently, PSL exposure may be altered by CYP3A4 inhibitors and inducers. It has already been demonstrated that concomitant administration of a strong CYP3A4 inducer (carbamazepine) significantly reduces exposure to PSL (UP0002).

UP0070 is a Phase 1, multicenter, open-label study in study participants with epilepsy, designed to evaluate the pharmacokinetic (PK) interaction between PSL and oxcarbazepine (OXC), a common AED that is known to have CYP3A4 induction potential (Spina et al, 1996), and could therefore have a negative impact on the efficacy of PSL if exposure is reduced significantly as a result.

The primary objective of UP0070 is to evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy) on the PK of PSL in study participants with epilepsy compared with study participants co-medicated with stable doses of levetiracetam (LEV), lamotrigine (LTG), or brivaracetam (BRV) therapy. The secondary objectives include the following: to evaluate the plasma concentrations of 10,11-dihydro-10-hydroxy-carbazepine (Mono Hydroxy Derivate [MHD]; circulating metabolite of OXC) before, during, and after administration of repeated doses of PSL, to evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy) on the plasma PK of PSL metabolites, [redacted] and [redacted], in study participants with epilepsy compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy, and to evaluate the safety and tolerability of PSL coadministration with stable OXC, LEV, LTG, or BRV therapy. The exploratory objectives include the following: to evaluate the plasma concentrations of LTG, LEV, and BRV before, during, and after administration of repeated doses of PSL and to evaluate and compare the venous blood and MITRA microsampling (dried blood) PK of PSL following administration of PSL study participants with epilepsy on stable coadministered OXC compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy.

UP0070 is comprised of the following periods: a Screening Period; a Treatment Period, and a Safety Follow-Up (SFU) Period. The study participants will remain on stable OXC (monotherapy or adjunctive to LEV, LTG, or BRV), LTG (monotherapy or adjunctive to LEV or BRV), LEV (monotherapy or adjunctive to LTG), or BRV (adjunctive to LTG) throughout the study. The Screening Period will occur within 28 days prior to the start of the Treatment Period. The Treatment Period consists of 12 days of PSL treatment increasing in dose from PSL 100mg twice daily (bid) to 400mg bid and then tapering back to 100mg bid. The SFU Period is performed 7 to 9 days after the last dose of investigational medicinal product (IMP) or upon discontinuation of the study.

2 INTRODUCTION

2.1 Background

More than 50 million people worldwide suffer from epilepsy. The prevalence in the UK is estimated to be 600,000 (JECUI, 2011; WHO, 2018).

A population-based study conducted in Western Europe estimated that 22.5% of all patients had drug-resistant epilepsy (Picot et al, 2008). Another population-based study of active and drug-resistant epilepsy in northern Italy, concluded that the frequency of drug-resistant epilepsy was 15.6% of all active epilepsies and 10.5% of incident cases (Giussani et al, 2016).

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, freedom from the risk of falls and injuries, and reach the milestones that most people take for granted: a feeling of belonging and social integration; the ability to form intimate relationships and a family; and having a productive and rewarding profession; or other means of self-realization.

Padsevonil is a novel chemical entity currently being developed clinically for the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy. The mechanism of action for PSL is unique in comparison to available AEDs because it has selective affinity both for presynaptic SV2 proteins and for postsynaptic cBZR sites on the gamma-aminobutyric acid type A ($GABA_A$) 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 sites offers robust protection against seizures.

The synergistic anticonvulsive effect observed when combining LEV, an AED that binds with SV2A, with benzodiazepines (BZDs) in preclinical models (Kaminski et al, 2009) was the motivation that led to the design of PSL. In nonclinical studies, PSL administered as a monotherapy has shown higher efficacy than LEV combined with a BZD (diazepam) at matching in vivo occupancies of SV2A and cBZR, respectively. This suggests that PSL's preclinical efficacy is not only due to the combination of these 2 mechanisms of action, but that a unique interaction of PSL with SV2 proteins may also play a role.

Padsevonil is cleared via metabolism involving the CYP pathway; the formation of the 2 major metabolites, [redacted] and [redacted], is mainly mediated by CYP3A4, with potential involvement of CYP2C19.

Studies in patients with refractory epilepsy showed that more than 60% of patients were treated concomitantly with 2 or more AEDs (Johannessen and Landmark, 2010). Drug-drug interactions that result in alterations in the PK of AEDs can have a profound impact on tolerability, efficacy, and safety, and can potentially result in toxicity. It is therefore important to consider and estimate at an early stage the possible interactions that may occur with the concomitant use of PSL and other drugs.

This study will evaluate the impact of an AED with known CYP3A4 inducing potential, OXC, on the PK of PSL in study participants with epilepsy, compared with the PK of PSL in a control group with coadministration of LEV, LTG, or BRV, which are not CYP-inducers.

2.2 Clinical studies and adverse event profile

As of 01 May 2018, PSL has been administered in 9 completed human Phase 1 pharmacology studies (N01360, N01383, N01386, UP0001, UP0002, UP0010, UP0013, UP0036, and UP0039) and 1 completed Phase 2 proof of concept study (EP0069). There is also 1 ongoing Phase 1 clinical pharmacology study (UP0057), 1 ongoing Phase 2 study (EP0091), 1 ongoing Phase 2 open-label extension study (EP0073), and 1 planned Phase 2 open-label extension study (EP0093). These studies have investigated the safety, PK, and pharmacodynamics (PD) of single and multiple ascending doses of PSL in both Caucasian and Japanese study participants, and the potential interaction of PSL with food, valproic acid, carbamazepine, and other AEDs. Positron-emission tomography investigations have been performed in healthy study participants to evaluate the $GABA_A$ receptor occupancy at 2 steady state PSL dose levels and SV2A occupancy at different single PSL dose levels and times postdose.

As of 06 Jun 2017, 129 healthy study participants and 20 patients with epilepsy (male and female) had been exposed to PSL at single doses up to 490mg (N=26 healthy study participants) and repeated doses up to 400mg bid for up to 12 days (N=103 healthy study participants and 20 patients) in the 7 completed Phase 1 studies. An additional 12 and 40 healthy study participants were exposed to at least 1 dose of PSL in the recently completed Phase 1 studies, UP0036 and UP0039, respectively. In the Phase 2 proof of concept study (EP0069), 55 study participants were exposed at doses up to 400mg bid during the maintenance phase of the study. A total of 42 of the 55 study participants enrolled in the open-label extension study (EP0073) during which they were allowed to adjust their PSL dose.

The safety findings to date suggest that the adverse events (AEs) experienced by study participants 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 across the Phase 1 and Phase 2 studies with PSL are consistent with the AE profile of other AEDs, including other SV2A ligands. Acute psychiatric effects occurred in 3 study participants administered PSL (2 in Phase 1 and 1 in Phase 2). The events were transient, acute, and required admission to psychiatric care and antipsychotic treatment. No definite dose relationship could be determined, and the events occurred after variable periods of time after the first administration of PSL. 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 significant psychiatric AEs and to maintain vigilance for them.

With regard to cardiovascular effects, minor, transient, reductions in blood pressure (BP) were observed in the Phase 1 and Phase 2 PSL 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 electrocardiogram (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 QT interval corrected for heart rate (QTc), or clinically-significant arrhythmia in clinical trials to date."

Echocardiographic screening of study participants at Baseline (to exclude study participants with valvulopathies) and ongoing echocardiographic monitoring during treatment and posttreatment have been implemented in the Phase 2 studies. No major findings were observed in the completed EP0069 study or the ongoing open-label extension study, EP0073. Cardiac monitoring (eg, ECGs, vital signs, echocardiograms) is planned throughout the duration of the PSL development program in order to better understand and mitigate any risks.

In general, the safety profile of PSL has been consistent with the pharmacological properties of the drug and with dose-escalation studies of CNS compounds 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, as well as preclinical and clinical experience with PSL, can be found in the Investigator's Brochure (IB).

2.3 Risk assessment

Safety pharmacology studies have shown no major adverse effects on the respiratory system and CNS when administered orally in single-dose safety pharmacology studies (rats) and in repeat dose toxicity studies (rats, dogs). A slight prolongation of QTc (≤10%) was found in a 4-week study in dogs and a single dose telemetry study at free plasma concentrations at least 6 times above the mean free peak plasma concentration reached in epilepsy patients at 30mg/kg bid; however, it was not confirmed in a 13-week study (animals monitored by external telemetry) or a 39-week study at doses up to 50mg/kg bid, with free plasma concentration far above those reached in epilepsy patients (up to 35-fold). Small, transient increases in heart rate and changes in arterial pressure (hypertension in rats and hypotension in dogs) occurring mainly from single doses are likely related to exaggerated $GABA_A$ pharmacologic activity.

Padsevonil administration was well tolerated in rats dosed up to 150mg/kg bid over 26 weeks and in dogs dosed up to 50mg/kg bid over 39 weeks using dose titration approach, providing safety margins versus human exposure at a dose of 400mg bid of 1.5 to 5 in rats and 42 in dogs. In rats, at higher dose levels, lower mean overall body weight gain, despite normal food consumption, accompanied by a decrease in bone length was observed and was considered to be adverse. Similar effects were not seen in female rats or in dogs.

In clinical studies, PSL had a good safety profile. There were no deaths. Adverse events experienced by study participants were limited principally to CNS effects and these were consistent with its known pharmacology, dose-related in frequency and intensity, self-limiting, and tended to decrease in intensity over the first few days of dosing.

The information obtained from this study will inform decisions on safe and effective doses of PSL to be given to study participants with epilepsy in future studies where PSL may be coadministered with other AEDs. The sponsor will immediately notify the Investigator and

regulatory agencies if any additional safety or toxicology information becomes available during the study.

2.3.1 Cardiovascular events

In the 39-week dog toxicity study, subtle cardiac microscopic findings, consisting of minimal valvular inflammatory cell infiltration, or minimal to slight epithelial inflammation/fibroplasia of the epicardium in the right atrium, were seen in the heart of one-third of treated dogs without dose relationship. Findings were subtle, minor, focal, and not associated with any changes in systemic cardiovascular parameters. They were not seen in any dog study of shorter duration. These findings did not cause any biological or clinical consequences in the animals in this study and were thus not considered to be adverse. These findings were not seen in the 13-week dog study. This conclusion was supported after comprehensive review of the data by 5 nonclinical pathologists (including a cardiovascular expert pathologist). Additionally, external advice on the potential human implications was sought from a British Heart Foundation Professor of Cardiology. It was concluded that short-term exposure should not lead to any relevant abnormality or clinical disease, and even with long-term exposure the potential hazard and likelihood of an adverse pericardial or valvular effect in humans is extremely low. Echocardiographic monitoring of study participants in the Phase 2 proof of concept study (EP0069) and its open-label extension (EP0073) was undertaken, and no major findings have been observed to date.

Despite the occurrence of ECG findings such as ectopies (asymptomatic, not requiring clinical intervention), there are no current data suggesting that PSL has an adverse effect on cardiovascular function other than a minimal lowering effect on BP. The degrees of reduction of both SBP and 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. As a precaution from preclinical and clinical findings of nonclinically significant ECG abnormalities and hypotension, ECGs and vitals are being assessed frequently in current clinical studies.

2.3.2 Psychiatric events

The occurrence of acute psychiatric serious adverse events (SAEs) (delirious syndrome, mania-like symptoms, and acute psychosis) in 3 study participants administered PSL highlights the need to maintain vigilance for such events. Reported acute psychiatric effects are consistent with adverse effects of other anticonvulsant drugs with various mechanisms of action. These SAEs were transient, acute, and required clinical intervention (admission to psychiatric care and antipsychotics). In healthy study participants, those SAEs occurred early after initiation of PSL done without titration; in 1 study participant, symptoms worsened upon abrupt drug discontinuation. Only in 1 out of 68 epileptic study participants exposed to PSL, a psychotic effect emerged a few weeks following dosing start after improvement in seizure control. This suggests a "forced normalization" phenomenon, which is described with other AEDs in resistant patients and is not unexpected with a potent AED (Loganathan et al, 2015; Clemens, 2005). The mitigation plan for acute psychiatric effects involves gradual titration and taper, known to improve tolerability of AEDs.

2.3.3 Interactions with other medicinal products

The preclinical pharmacology studies indicated that the metabolism of PSL may be affected by extrinsic influences on the CYP3A4/CYP2C19 pathway. In order to mitigate any risk caused by

these interactions, medication or dietary ingredients that induce, inhibit, or are a substrate for the CYP3A4/CYP2C19 pathways are restricted. Further details are provided in Section 7.8.1 and Section 7.8.2.

2.3.4 Pregnancy and lactation

Padsevonil is neither teratogenic nor embryotoxic in rats and rabbits. There was no effect on reproductive organs, including sperm analysis, following long-term administration (up to 26 weeks in rats and 39 weeks in dogs). Padsevonil has not been studied in pregnant or lactating women, and the effects of PSL on the developing embryo/fetus in humans are unknown; therefore it should not be administered to women of childbearing potential unless they are using stringent measures of birth control.

Additional details regarding risks can be found in the IB.

2.4 Urgent safety measures

In accordance with UK Law (Medicines for Human Use [Clinical Trials] as amended: SI 1031 Part 4 Section 30), the sponsor and Investigator may take appropriate urgent safety measures in order to protect the study participants of a clinical study against any immediate hazard to their health or safety. If such measures are taken, the sponsor shall immediately (no later than 3 days from the date the measures are taken) give written notice of the measures taken and the circumstances giving rise to those measures to the licensing authority and the relevant ethics committee.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy) on the PK of PSL in study participants with epilepsy compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy.

3.2 Secondary objectives

The secondary objectives of this study are to:

- Evaluate the plasma concentrations of MHD (circulating metabolite of OXC) before, during, and after administration of repeated doses of PSL
- Evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy), on the plasma PK of PSL metabolites, [redacted] and [redacted], in study participants with epilepsy compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy.
- Evaluate the safety and tolerability of PSL coadministration with stable OXC, LEV, LTG, or BRV therapy

3.3 Exploratory objectives

The exploratory objectives of this study are to:

- Evaluate the plasma concentrations of LTG, LEV, and BRV before, during, and after administration of repeated doses of PSL. (Blood samples for plasma concentrations of LEV,

LTG, and BRV samples will be collected and stored during the study; they will only be measured on an as-needed basis.)

- Evaluate and compare the venous blood and MITRA microsampling (dried blood) PK of PSL following administration of PSL in study participants with epilepsy on stable coadministered OXC compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy.

4 STUDY VARIABLES

4.1 Pharmacokinetic variables

4.1.1 Primary pharmacokinetic variables

The primary PK variables will comprise C_{max}, t_{max}, AUC_{τ}, and CL/F_{ss} obtained from the plasma concentration-time profiles for PSL:

- C_{max}: maximum observed plasma concentration
- t_{max}: time of maximum concentration
- AUC_{τ}: area under the curve over a dosing interval (12 hours)
- CL/F_{ss}: apparent total clearance at steady-state

4.1.2 Secondary pharmacokinetic variables

The secondary PK variable will be the trough plasma concentration of MHD (OXC metabolite) before, during, and after dosing to steady state with PSL.

Additionally, the secondary PK variables for PSL metabolites ([redacted] and [redacted]) will comprise C_{max}, t_{max}, AUC_{τ}, and the ratio of metabolite to PSL based on AUC_{τ}.

4.1.3 Other pharmacokinetic variables

The following other PK variables will be assessed during the study:

- Trough plasma concentrations of LEV, LTG, or BRV before, during, and after dosing to steady state with PSL
- Comparison of plasma concentrations from MITRA microsampling (dried blood) with venous sampling for PSL

4.2 Safety variables

4.2.1 Secondary safety variables

The following secondary safety variables will be assessed during the study:

- Incidence of AEs and SAEs

4.2.2 Other safety variables

The following other safety variables will be assessed during the study:

- Changes in vital signs (pulse rate [PR], respiratory rate [RR], SBP, and DBP)

- Changes in clinical laboratory test results (hematology, serum chemistry, and urinalysis)
- Changes in 12-lead ECG parameters
- Physical examination findings

5 STUDY DESIGN

5.1 Study description

This is a Phase 1, multicenter, open-label study in study participants with epilepsy, to evaluate the effect of OXC on the PK and safety and tolerability of PSL.

A total of 28 study participants will be evaluated in the following 2 groups (14 study participants per group):

- Group 1 (Inducers): study participants on stable therapy with OXC (at least 1200mg/day either as monotherapy or adjunctive to LEV, LTG, or BRV). Oxcarbazepine may be used as monotherapy (at least 7 study participants) or in combination with 1 or more of LEV, LTG, or BRV). (For adjunctive therapy, the dosing of each AED in the combination [OXC+LEV, OXC+BRV, or OXC+LTG] must be within the range used per label.)
- Group 2 (Neutral [control]): study participants on stable therapy with LTG (at least 150mg/day monotherapy or adjunctive to LEV or BRV), LEV (at least 1g/day monotherapy or adjunctive to LTG), or BRV (up to 200mg/day adjunctive to LTG). Lamotrigine or LEV may be used as monotherapy (at least 7 study participants) or in combination with each other. Brivaracetam may only be used in combination with LTG. (For adjunctive therapy, the dosing of each AED in the combination [LTG+LEV or LTG+BRV] must be within the range used per label.)

Padsevonil will be dosed to steady state (4.5 days) in both groups and the effect of background therapy on PSL PK will be assessed at steady state.

5.2 Study Periods

5.2.1 Screening Period

The Screening Period consists of a single Screening Visit, which will be conducted at the unit within 28 days prior to check-in for the Treatment Period, and a Baseline Visit, which will be conducted at the unit 1 day prior to the Treatment Period.

A sufficient number of study participants with epilepsy will be screened to ensure that 14 study participants are included in each group.

In Group 1 (study participants taking stable coadministered OXC), OXC may be used as monotherapy (at least 7 study participants) or in combination with 1 or more of LEV, LTG, or BRV). (For adjunctive therapy, the dosing of each AED in the combination [OXC+LEV, OXC+BRV, or OXC+LTG] must be within the range used per label.)

In Group 2 (study participants taking LTG, LEV, or BRV), LTG or LEV may be used as monotherapy (at least 7 study participants) or in combination with each other. Brivaracetam may only be used in combination with LTG. (For adjunctive therapy, the dosing of each AED in the combination [LTG+LEV or LTG+BRV] must be within the range used per label.)

5.2.1.1 Screening Visit (Day -28 to Day -2)

Study participants are required to sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure. Screening assessments will be conducted, after which the eligibility of study participants will be determined based on: inclusion and exclusion criteria (see Section 6.1 and Section 6.2, respectively); demographics; medical history; full physical examination (including weight and height); medication history; vital sign measurements; several laboratory tests (hematology, serum chemistry, urinalysis, serology screening, alcohol breath test, and urine toxicology screen); triplicate 12-lead ECGs; and recording of AEs/medical procedures. A serum pregnancy test will be performed to assess eligibility for women of childbearing potential.

5.2.1.2 Baseline Visit (Day -1)

At the Baseline Visit, study participants will check in at the unit the afternoon prior to the visit and receive a study participant Identification Card.

The following procedures/assessments will be repeated: inclusion/exclusion criteria verification; medical history; full physical examination; medication history; vital sign measurements; laboratory tests (hematology, serum chemistry, urinalysis, alcohol breath test, and urine toxicology screen); triplicate 12-lead ECGs; and recording of AEs/medical procedures. A urine pregnancy test will be performed to assess eligibility for women of childbearing potential. Study participants will also be assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal risk.

Study participants can then be discharged from the unit after all procedures/assessments have been completed. The study participants may continue being confined to the unit at the Investigator's discretion or continue the study ambulatory until the afternoon of Day 7.

5.2.2 Treatment Period

The Treatment Period consists of 3 days of dose titration (Day 1, Day 2, and Day 3), 4.5 days of PSL maintained at a stable dose (Days 4 through 7 and the morning of Day 8), and 4.5 days of dose taper (evening of Day 8 and Days 9 through 12).

The dose titration (Day 1, Day 2, and Day 3) will be initiated as follows: all study participants enrolled into the study will receive 1 day of PSL 100mg bid followed by 2 further days of PSL 200mg bid. Padsevonil 400mg will then be maintained by oral administration bid on Day 4 through Day 7 and once on Day 8 in the morning. Ambulatory study participants will be readmitted to the unit on the afternoon of Day 7. All dosing must be observed, ie, the study participants must return to the unit for the predose meal and dosing morning and evening, unless arrangements can be made for home visits with the same requirements.

A dose taper will be initiated on the evening of Day 8, when study participants will be administered PSL 200mg. On Day 9 and Day 10, PSL 200mg bid will be administered. On Day 11 and Day 12, PSL 100mg bid will be administered.

The following procedures/assessments will be completed: C-SSRS (for ambulatory study participants only on Day 1 through Day 7); prior and concomitant medication; vital sign measurements; triplicate 12-lead ECGs; and recording of AEs/medical procedures.

5.2.3 Safety Follow-Up Period

Study participants will be discharged on Day 13 and return for an End of Study (EOS) Visit on Day 20±1.

The SFU Period consists of discharge from the unit on Day 13 and an EOS Visit performed on Day 20±1 or upon discontinuation of the study. Study participants will have the following procedures/assessments completed at the EOS Visit: C-SSRS; a full physical examination; prior and concomitant medication; vital sign measurements; laboratory safety (hematology, serum chemistry, and urinalysis); triplicate 12-lead ECGs; and recording of AEs/medical procedures. A urine pregnancy test will also be administered for woman of childbearing potential.

5.3 Pharmacokinetic sampling

Study participants will undergo serial blood sampling to measure plasma concentrations of PSL, PSL metabolites ([redacted] and [redacted]), and OXC metabolite (MHD), as well as safety monitoring. Blood samples for plasma concentrations of LEV, LTG, and BRV samples will be collected and stored during the study; they will only be measured on an as-needed basis. Pharmacokinetic analysis will be performed using both conventional plasma as well as contemporaneous MITRA microsampling (dried blood) of PSL to compare the 2 methods.

5.3.1 Venous blood

Venous blood samples for PK analysis will be collected as follows:

- Padsevonil and PSL metabolites ([redacted] and [redacted]):
  - prior to the morning dose of PSL on Day 1 through Day 7 and Day 9 through Day 13
  - prior to the morning dose of PSL and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h after administration of the morning dose of PSL (prior to the evening dose) on Day 8
- AEDs: trough samples prior to the morning dose of the AED(s) on Day -1, Day 1 through Day 13, and the EOS Visit

5.3.2 Microsamples of capillary blood

Samples for PK of PSL from a finger skin prick will be collected using the MITRA device, as close to the conventional PK sampling as possible, at each of the time points identified for the venous blood samples for Day 8 in Section 5.3.1.

5.4 Study duration per study participant

The maximum total duration of the study is 49 days (7 weeks) for each study participant, including the Screening Period (up to 28 days), Treatment Period (12 days), and the SFU Period (maximum of 9 days).

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

5.5 Planned number of study participants and sites

A total of 28 evaluable study participants are planned to be enrolled at a minimum of 2 sites. If a study participant drops out before completing the key assessments (ie, the full PK profile on Day 8), the study participant will be replaced.

5.6 Anticipated regions and countries

This study will be conducted in the Netherlands, Bulgaria, and Germany (and potentially other countries in Europe).

5.7 Schedule of study assessments

The schedule of assessments is presented in Table 5-1.

Table 5-1: Schedule of study assessments

Procedures	Screening Period		Treatment Period				SFU Period	
	Screening	Baseline	Titration	Maintenance		Taper	SFU Post-treatment	EOS/ET [a]
	Day -28 to Day -2	Day -1	Days 1-3 (Ti1-Ti3)	Days 4-7 (M1-M4)	Day 8 [e] (M5/Ta1)	Days 9-12 [e] (Ta2-Ta5)	Day 13	Day 20 (±1)
Written Informed Consent	X							
Record info on habits and lifestyle	X							
Demographics & baseline characteristics	X							
Inclusion/Exclusion criteria verification	X	X						
General medical/procedures history	X	X						
Enrollment to Inducers or Neutral (control) Group		X						
Study Participant Identification Card assigned		X						
Psychiatric History	X							
Administer C-SSRS [b]		X	X[c]	X[c]			X	X
Physical examination	X	X					X	X
Prior and concomitant medications	X							
Record intake of grapefruit, starfruit, or pawpaw (as beverage, fruit, or supplements) [d]			X	X	X	X		
Blood sample for MHD plasma level [e]	X	X	X	X	X	X	X	X
Pregnancy test [f]	X	X						X

Table 5-1: Schedule of study assessments

Procedures	Screening Period		Treatment Period				SFU Period	
	Screening	Baseline	Titration	Maintenance		Taper	SFU Post-treatment	EOS/ET [a]
	Day -28 to Day -2	Day -1	Days 1-3 (Ti1-Ti3)	Days 4-7 (M1-M4)	Day 8 [e] (M5/Ta1)	Days 9-12 [e] (Ta2-Ta5)	Day 13	Day 20 (±1)
Hematology, serum chemistry, urinalysis	X	X					X	X
Serology (HIV, Hepatitis B & C)	X							
Vital signs [g]	X	X	X	X	X	X	X	X
12-lead ECG [g]	X	X[h]	X	X	X[h]	X	X	X
Height/weight, BMI	X							
Drug/alcohol screen	X	X						
Recording of adverse events/medical procedures	X							
Admit to study center		X		X				
Discharge from study center		X					X	
Dispense Padsevonil [i]			X	X	X	X		
Study drug accountability			X					
Blood sample for AED trough level [j]		X	X	X	X	X	X	X
Blood sampling for PSL and metabolites PK levels			X[k]	X[k]	X[l]	X[k]	X[k]	
Final Disposition Determination								X

AED=antiepileptic drug; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOS/ET=End of Study/Early Termination; h=hour(s); HIV=human immunodeficiency virus; IMP=investigational medicinal product; M=Maintenance; Mono Hydroxy Derivate; OXC=oxcarbazepine; PK=pharmacokinetic(s); PSL=Padsevonil; SFU=Safety Follow-Up; Ta=Taper; Ti=Titration

Note: Day –1 is defined as the day before Day 1. Day 1 is defined as the first day of administration.

Note: For study participants prematurely terminating or completing the study, final disposition is recorded at EOS/ET. All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures, in accordance with the EOS/ET schedule, as soon as possible after the last dose of study drug.

Note: Study participants will be admitted to the unit on the afternoon prior to Day -1 for baseline assessments and can be discharged after the last ECG assessment (6h). They will be readmitted to the unit on the afternoon of Day 7 and will be discharged from the unit on Day 13 in the morning after completion of all procedures/assessments. During visits on Day 1 through Day 7, ambulatory study participants to will come to the unit at least 2 hours prior to the morning dose and remain until completion of all procedures/assessments. They should return to the unit at least 1 hour prior to the evening dose.

[a] The SFU assessments should be performed for any study participant who withdraws from the study 7 to 9 days after the last dose of PSL.

[b] At the Baseline Visit, complete the "Baseline/Screening" version of the C-SSRS. At all other visits, complete the "Since Last Visit" version of the C-SSRS.

[c] Only for ambulatory study participants.

[d] Grapefruit, starfruit, and pawpaw (as beverage, fruit, or supplements) within 72 hours before first administration of IMP, during the Treatment Period, and throughout the study will not be allowed. If this is the case at the start of the study, study participation may be delayed as long as it occurs within the screening window.

[e] This is only done for study participants taking OXC. If the study participant administers OXC in the morning and evening, the blood sample should be obtained prior to the morning dose of OXC. If the study participant administers OXC once daily, then the blood sample should be obtained just prior to the daily dose. At the Screening Visit, the blood sample must be collected no later than on Day -7 (with MHD reassessment, if required, no later than Day -4); other safety assessments including reassessments are allowed no later than Day -2.

[f] A serum pregnancy test will be performed at Screening for women of childbearing potential only. A urine pregnancy test will be performed at Baseline and at EOS/ET for women of childbearing potential only.

[g] Triplicate 12-lead ECGs and vital signs (after a rest of at least 5 minutes at 2- to 3-minute intervals) will be performed on Days 1 through 12, prior to the PK collection prior to the morning dose of PSL.

[h] Triplicate 12-lead ECG (after a rest of at least 5 minutes at 2- to 3-minute intervals) will be taken shortly prior to each of the following PK collection time points at Day 8: predose, 0.5h, 1h, 2h, 3h, 6h, and 12h post the morning dose of PSL. In addition, 1 day prior to the first dose of PSL on Day -1 (Baseline) triplicate 12-lead ECGs will be performed after a rest of at least 5 minutes at 2- to 3-minute intervals for each of the following matching time points: predose, 0.5h, 1h, 2h, 3h, and 6h postdose for the morning administration of PSL, and 0.5h predose for the evening administration of PSL, where dosing time is equivalent to the expected time of dosing on Day 8.

[i] Investigational medicinal product will be administered bid 12h apart each day. All study participants enrolled into the study will receive 1 day of PSL at 100mg bid (Day 1) followed by 2 further days at 200mg bid (Day 2 and Day 3). Padsevonil 400mg will then be administered orally bid on Day 4 through Day 7 and once on Day 8 in the morning. A dose taper will be initiated on the evening of Day 8, when study participants will be administered an evening dose of PSL 200mg. Padsevonil 200mg bid will be administered on Day 9 and Day 10. Padsevonil 100mg bid will be administered on Day 11 and Day 12.

[j] Obtain blood samples for storage; measurement of the trough level of the concomitant AED will be done as needed. If the study participant administers the concomitant AED in the morning and evening, the blood sample should be obtained prior to the morning dose of the AED (and on applicable days, prior to the morning dose of PSL). If the study participant administers the concomitant AED once daily, then the blood sample should be obtained just prior to the daily dose (and if applicable, prior to the dose of PSL).

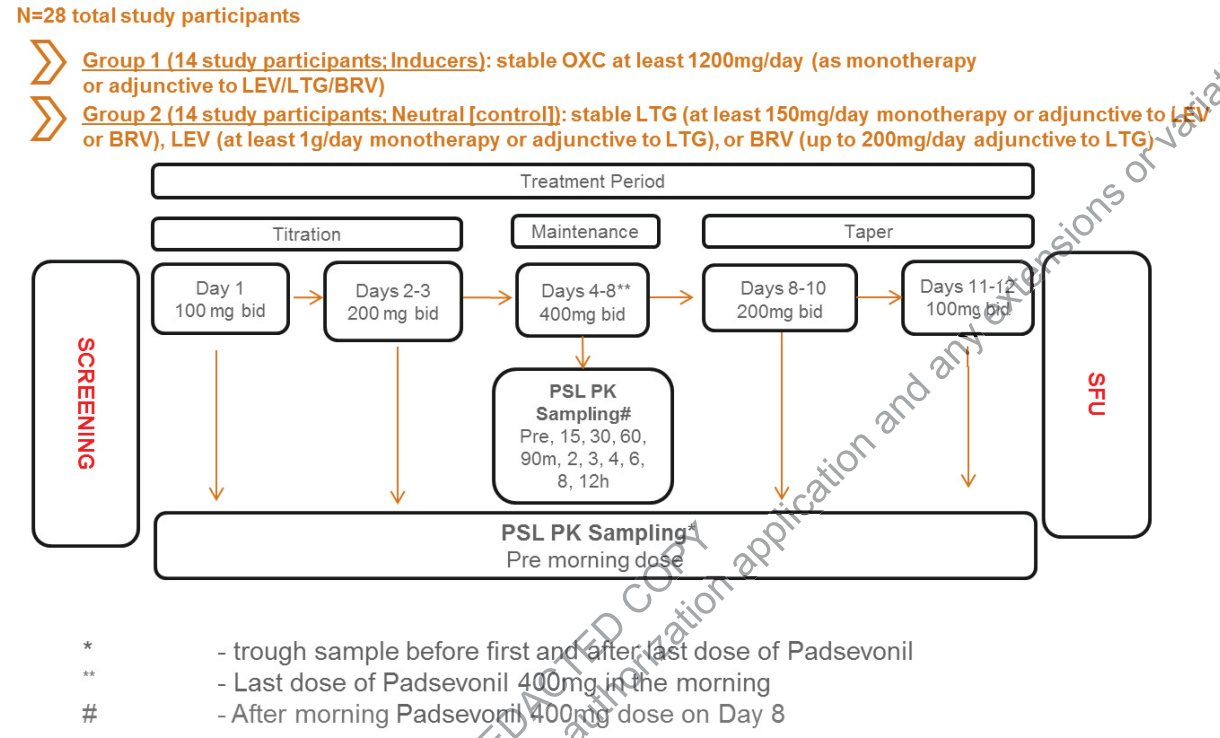
[k] Obtain blood samples (venous only) for measurement of trough levels of PSL and metabolites just prior to the morning dose of PSL on Day 1 through Day 12. On Day 13, sampling should occur prior to discharge.

[1] Obtain blood samples (venous and MITRA) for measurement of plasma concentration of PSL at the following times: predose (within 5min of dosing), then at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose. Time windows for postdose samples are as follows: ±5min for the 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, and 4h samples; ±10min for the 6h, 8h, and 12h samples. The 12h sample must be obtained prior to the evening dose.

5.8 Schematic diagram

The study schematic diagram for UP0070 is presented in Figure 5-1.

Figure 5-1: Schematic diagram



bid=twice daily; BRV=brivaracetam; LEV=levetiracetam; LTG=lamotrigine; OXC=oxcarbazepine
PK=pharmacokinetic(s); PSL=Padsevonil; SFU=Safety Follow-Up; T=Titration

5.9 Rationale for study design and selection of dose

In an earlier study (UP0002), carbamazepine (CBZ, a strong CYP3A4 inducer) was demonstrated to reduce PSL exposure by >80% compared with a control group where coadministration of non-inducing AED drugs (LEV/LTG) had no impact on PSL exposure. Oxcarbazepine is a known CYP3A4 inducer with less potency compared with CBZ (Andreasen et al, 2007). The primary objective of this study is to evaluate the effect of stable coadministered OXC on the PK of repeated doses of PSL 400mg bid in study participants with epilepsy, compared with study participants co-medicated with stable doses of LEV, LTG, or BRV therapy.

The PSL dose will be 400mg bid (the maximum intended therapeutic dose and hence highest exposure), which demonstrates no safety concerns in the patient population and provides a comparison with previous studies performed with this dose (UP0002).

6 SELECTION AND WITHDRAWAL OF STUDY PARTICIPANTS

6.1 Inclusion criteria

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

1. An Independent Ethics Committee (IEC) approved written ICF is signed and dated by the study participant.
2. Study participant 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. Study participant is male or female between 18 to 64 years of age, inclusive, with a diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) classification (Fisher et al, 2014).
4. Study participant is currently treated for epilepsy with stable doses of the following for at least 3 months:
   a) Inducers Group: OXC (at least 1200mg/day as monotherapy or in combination with BRV [up to 200mg/day], LEV [at least 1g/day] or LTG [at least 150mg/day]); or
   b) Neutral (control) Group: LTG (at least 150mg/day monotherapy or adjunctive to LEV or BRV), LEV (at least 1g/day monotherapy or adjunctive to LTG), or BRV (up to 200mg/day adjunctive to LTG).
5. Study participant in the Inducers Group is taking OXC and has a trough OXC metabolite (MHD) plasma level in the target range (≥12.0 to ≤35.0 mcg/mL). At the Screening Visit, the blood sample must be collected no later than on Day -7 (with MHD reassessment, if required, no later than Day -4).
6. Study participant is in generally good physical and mental health, in the opinion of the Investigator, determined on the basis of medical history and a general clinical examination at the Screening Visit (ie, study participant has no current or past medical history of clinical significance, other than epilepsy, that would mitigate against their participation in the study).
7. Study participant has clinical laboratory test results within the local reference ranges or values are considered as not clinically relevant by the Investigator and approved by the UCB Study Physician. Laboratory parameters outside the reference ranges can be retested and if the retest result is within the reference range or considered as clinically not relevant the study participant is allowed in the study. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) should be within the normal limits. Liver enzymes up to 25% above the upper limit may be repeated once and should be within normal limits before inclusion.
8. Study participant has a body mass index (BMI) of 18 to 35kg/m², inclusive, with a body weight of at least 50kg (male) or 45kg (female).
9. Study participant has BP and PR within normal range in the supine position after 5 minutes rest (SBP: 90mmHg to 145mmHg, DBP: 40mmHg to 95mmHg, PR: 40bpm to 100bpm).

Any values outside the normal range, but considered not clinically significant by the Investigator, are allowed.

10. Female study participant has a negative serum pregnancy test at the Screening Visit and agrees to use an efficient form of contraception for the duration of the study (unless menopausal [defined as no menses for 12 months without an alternative medical cause]; a high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy). 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 methods requires that a barrier method (preferably male condom) also be used.

    Birth control methods considered as an efficient form of contraception:

    - Combined (oestrogen and progestogen containing) hormonal contraception (oral, implant, or injectable) associated with inhibition of ovulation in combination with a barrier method (preferably male condom)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation in combination with a barrier method (preferably male condom)
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS) in combination with a barrier method (preferably male condom)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence

      True 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, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
    - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action in combination with a barrier method (preferably male condom)
    - Male or female condom with spermicide (ie, double barrier)
    - Cap, diaphragm, or sponge with spermicide

      To ensure proper birth control, females who use hormonal contraception should use an efficient barrier contraceptive in the 3 months following the end of the study (ie, for 3 months after the last intake of study medication).

11. Male study participant agrees that, during the study period, when having sexual intercourse with a woman of childbearing potential, he will use an efficient barrier contraceptive (condom plus spermicide) AND that the respective partner will use an additional efficient contraceptive method (eg, oral pills, IUDs, IUSs, or diaphragm, and spermicide).

6.2 Exclusion criteria

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

1. Study participant has previously received the IMP administered in this study.
2. Study participant has participated in another study of an investigational medication (or a medical device) within the last 3 months before screening (or 5 half-lives, whichever is longer) or is currently participating in another study of an investigational medication (or a medical device).
3. Study participant has a known hypersensitivity to any components of the IMP as stated in this protocol
4. Study participant has a current or past psychiatric condition that, in the opinion of the Investigator, could compromise his/her safety or ability to participate in this study or a history of schizophrenia, or other psychotic disorder, bipolar disorder, or severe unipolar depression. The presence of potential psychiatric exclusion criteria will be determined based on the psychiatric history collected at the Screening Visit.
5. Study participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has had 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 C-SSRS at the Baseline Visit.
6. Study participant has any medical condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
7. Study participant has a history of status epilepticus during the last year.
8. Study participant has a history or presence of drug or alcohol dependency or tests positive for alcohol and/or drugs at the Screening Visit or Day -1.
9. Study participant has a consumption of more than 3 units of alcohol/day in case of females, more than 4 units of alcohol/day in case of males.
10. Study participant smokes more than 5 cigarettes per day (or equivalent) or has done so within 6 months prior to the Screening Visit.
11. Study participant has a consumption of more than 600mg of caffeine/day within 7 days prior to the Baseline Visit and does not agree to limit consumption below this limit for the duration of the study (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg).
12. Study participant ingests grapefruit, starfruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before first administration of IMP. These fruits are not allowed during the Treatment Period and throughout the study.

13. Study participant has either:
    - >2.0x upper limit of normal (ULN) of any of the following:
        - ALT
        - AST
        - ALP

    -OR-

    - ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome).

    If study participant 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 study participant 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 study participant 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 study participant must be discussed with the UCB Study Physician.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. If out of range again, the study participant cannot be included.

14. Study participant has made a blood or plasma donation or has had a comparable blood loss (>400mL) within the last 3 months prior to the Screening Visit.
15. Study participant has a history or present condition of respiratory or cardiovascular disorders, eg, cardiac insufficiency, coronary heart disease, hypertension, arrhythmia, tachyarrhythmia, or myocardial infarction.
16. Study participant has any clinically relevant ECG finding at the Screening Visit or at Baseline. Study participant has an abnormality in the 12-lead ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett's formula (QTcB) or Fridericia's formula (QTcF) >450ms in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval ≥220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out of range result, 1 repeat will be allowed. If out of range again, the study participant cannot be included.
17. Study participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
18. Study participant tests positive for human immunodeficiency virus-1/2 antibody (HIV-1/2Ab), hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCV-Ab).
19. Female study participant tests positive for pregnancy, plans to get pregnant during the participation in the study, or is breastfeeding.

20. Study participant has received any prescription or nonprescription medicines, including enzyme inhibitors or inducers, over the counter (OTC) remedies, herbal and dietary supplements (including St. John's Wort), or vitamins up to 2 weeks or 5 half-lives of the respective drug (whichever is longer) before the first administration of IMP and during the clinical part of the study, unless required to treat an AE. This does not include allowed AEDs per the protocol, oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants).

6.3 Withdrawal criteria

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

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

1. Study participant develops a clinically relevant medical condition (physical or psychiatric) that would interfere with his/her continued participation.
2. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Study participant takes prohibited concomitant medications as defined in this protocol.
4. Study participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The sponsor or a regulatory agency requests withdrawal of the study participant.
7. Subject has active suicidal ideation without specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The study participant 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 study participant 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 study participant should be referred immediately to a mental healthcare professional and must be withdrawn from the study.
8. Refer to Section 6.4.3 for withdrawal criteria in relation to potential drug-induced liver injury (PDILI).

Investigators should attempt to obtain information on study participants in the case of withdrawal. For study participants considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the study participant), 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 study participant, must be

recorded in the source documents. The eCRF (electronic Case Report form) must document the primary reason for withdrawal.

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

6.4 Stopping rules

6.4.1 Individual study participants

Should a study participant experience an AE meeting any of the following criteria, then IMP dosing in that individual will be suspended:

- possibly drug-related SAE
- severe, possibly drug-related AE or new laboratory or other finding of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 lasting longer than 12 hours (ie, still present at the time of the next scheduled dose)
- moderate, possibly drug-related AE or new laboratory parameter abnormality or other finding of Grade ≥2 lasting for longer than 72 hours
- any AE considered severe enough by the Investigator to pose a significant threat to the study participant's safety

Dosing will remain suspended in that study participant until the Investigator and UCB Study Physician have met to consider whether or not dosing may be resumed, based on the evolution of the event and any relevant clinical or laboratory findings.

6.4.2 All study dosing

Dosing of all study participants in the study will be suspended if:

- Two or more study participants meet 1 or more of the individual stopping criteria due to AEs in the same System Organ Class (SOC) classification or laboratory parameter class and (following assessment by the UCB Study Physician and Investigator) are not permitted to resume dosing.
- Despite the above study stopping criterion not being met, a pattern of suitably concerning AEs, laboratory test abnormalities, or other findings is identified that, in the opinion of the Investigator and/or UCB Study Physician, indicates that continued dosing is not justifiable under the current protocol on safety grounds.

Once dosing has been suspended in the study, as a whole, it will not be resumed prior to submission of an amended protocol and approval by the appropriate Regulatory Authority and Ethics Committee.

6.4.3 Potential drug-induced liver injury IMP discontinuation criteria

Study participants with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criterion below requires immediate and permanent discontinuation of IMP:

- Study participants with ≥3xULN ALT or AST

Evaluation of PDILI must be initiated as described in Section 10.6.1. If study participants are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on study participants in the case of IMP discontinuation to complete the final evaluation. Study participants 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 study participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation

7 STUDY TREATMENT

7.1 Description of investigational medicinal product

Padsevonil (100mg tablets) will be supplied by UCB.

7.2 Treatment to be administered

Padsevonil will be administered orally with 8oz (240mL) water, 30 minutes after a light or standard meal for the morning dose and 30 minutes after a standard meal for the evening dose, according to Table 7-1.

Table 7-1: Padsevonil administration

Day	Morning dose	Evening dose
1 (Ti1)	100mg	100mg
2 (Ti2)	200mg	200mg
3 (Ti3)	200mg	200mg
4-7 (M1-M4)	400mg	400mg
8 (M5/Ta1)	400mg	200mg
9 (Ta2)	200mg	200mg
10 (Ta3)	200mg	200mg
11 (Ta4)	100mg	100mg
12 (Ta5)	100mg	100mg

M=Maintenance; Ta=Taper; Ti=Titration

Treatments will be administered in an open-label fashion. Study participants will continue to take OXC, LTG, LEV, or BRV as per their usual regimen.

7.3 Packaging

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

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.

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 regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

The Investigator (or designee) will instruct the study participant 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- study participant 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/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 study participant compliance

Administration of PSL will be performed under the supervision of the Investigator (or designee), and the Investigator (or designee) will check the study participant's hands and the oral cavity immediately after dosing to confirm ingestion of the IMP. All dosing must be observed, ie, the study participants must return to the unit for the predose meal and dosing morning and evening, unless arrangements can be made for home visits with the same requirements. Compliance will be monitored by drug accountability and by drug assay (using the drug concentration in the

blood). Compliance with the IMP is defined as consumption by the study participant that conforms 100% with the planned dosage.

Drug administration/consumption will be recorded and any discrepancies with the dosing regimen must be explained.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

Study participants will continue to take a minimum of OXC (at least 1200mg/day), BRV (up to 200mg/day), LTG (at least 150mg/day), or LEV (at least 1g/day) as per their usual regimen.

The following concomitant medications are permitted during the study:

- Paracetamol for the treatment of mild symptoms (eg, headache or other pain), given at most every 6h to 8h, not exceeding 2g/day, and with a total of no more than 5g over 7 days.
- Ibuprofen
- Inhaled corticosteroids for seasonal rhinitis

7.8.2 Prohibited concomitant treatments (medications and therapies)

With the exception of permitted concomitant treatments listed above all prescription or nonprescription medicines, including OTC remedies and herbal and dietary supplements (including St John's Wort), are prohibited within 14 days or 5 half-lives (whichever is longer) before administration of PSL and during the Treatment Period, unless required to treat an AE. Drugs of unknown half-life are prohibited within 14 days before administration of PSL and during the Treatment Period, unless required to treat an AE.

7.8.3 Rescue medication

There are no absolute restrictions on the use of concomitant medications to "rescue" study participants whose seizure control significantly deteriorates during the course of the study. While the objectives of the study should be protected as much as possible through observance of the restrictions detailed in Section 7.8.2, the well-being of the study participant will always take priority, and study participants should be managed as deemed appropriate by the Investigator. If use of any prohibited medications is anticipated, this should be discussed with the UCB Study Physician first, wherever possible.

7.8.4 Diet, fluid, and activity control

During the Treatment Period, study participants will complete a light meal 30min prior to each morning dose of IMP, and a standard meal 30min prior to each evening dose of IMP.

Study participants should keep their usual diet (besides the restrictions for the study) necessary for the maintenance of good health; excessive food consumption should be avoided. Study participants should refrain from heavy physical exertion (eg, vigorous exercise) from 3 days prior to (first) confinement and during the study.

Study participants should not consume more than 3 units alcohol/day (females) and 4 units alcohol/day (males), or more than 600mg of caffeine/day (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola

approximately 20mg) from 48 hours prior to each administration of PSL and until the final PK plasma sampling of the Treatment Period.

Grapefruit, starfruit, and pawpaw (as beverage, fruit, or supplements) within 72 hours before first administration of IMP, during the Treatment Period, and throughout the study will not be allowed. If this is the case at start of study, study participation may be delayed as long as it occurs within the screening window.

Study participants must refrain from donating blood or plasma during the course of the study (except for the samples taken for the purpose of the study) and should refrain from donating blood or plasma for at least 3 months prior to the Screening Visit and until 2 months after the end of the study.

Water will be available ad libitum except for between 1 hour before and 2 hours after dosing. A total of 240mL of water will be given to each study participant at the time of administration of IMP.

7.9 Blinding

UP0070 is an open-label study; thus there will be no blinding.

7.10 Numbering of study participants

Each study participant will receive a unique 5-digit number assigned at Screening that serves as the study participant identifier throughout the study. If the study participant withdraws or is withdrawn from the study, this number will not be reassigned to another study participant.

8 STUDY PROCEDURES BY VISIT

8.1 Screening Period (Day -28 to Day -1)

8.1.1 Screening Visit (Day -28 to Day -2)

The Screening Visit will be conducted at the unit within 28 days prior to the first day of treatment. The following procedures/assessments will be performed:

- Written Informed Consent
- Demographics, habits, and lifestyle
- Inclusion/exclusion criteria verification
- General medical/psychiatric/procedures history
- Full physical examination, including height and weight
- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, DBP, and oral temperature)
- Triplicate 12-lead ECGs (prior to collection of PK samples)
- Blood samples (venous) for trough PK analysis (prior to OXC morning dose):
  - MHD plasma level (only for study participants taking OXC)

- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Serum pregnancy test (for women of childbearing potential only)
  - Hematology, serum chemistry, and urinalysis
  - Serology screening
  - Urine drug screen
- Alcohol breath test
- Recording of AEs/medical procedures

8.1.2 Baseline Visit (Day -1)

Study participants will check in to the unit on the afternoon prior to this visit and will be assigned their Study Participant Identification Card. The following procedures/assessments will be performed before discharge:

- Inclusion/exclusion criteria verification
- General medical/procedures history
- Enrollment to Inducers or Neutral (control) Group
- Dispense Study Participant Identification Card
- C-SSRS ("Baseline/Screening" version of the C-SSRS)
- Full physical examination
- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, DBP, and oral temperature)
- Triplicate 12-lead ECGs
  - Morning: approximately 0.5h prior to the expected time of the morning dose on Day 8, and 0.5h, 1h, 2h, 3h, and 6h after the expected time of the morning dose on Day 8
  - Evening: approximately 0.5h prior to the expected time of the evening dose on Day 8
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Hematology, serum chemistry, and urinalysis
  - Urine pregnancy test (for women of childbearing potential only)
  - Urine drug screen
- Alcohol breath test
- Recording of AEs/medical procedures

8.2 Treatment Period (Day 1 to Day 12)

8.2.1 Titration Period

8.2.1.1 Day 1 to Day 3

Study participants may continue being confined to the unit at the Investigator's discretion or continue the study ambulatory until the afternoon of Day 7. All dosing must be observed, ie, the study participants must return to the unit for the predose meal and dosing morning and evening, unless arrangements can be made for home visits with the same requirements. All study participants enrolled into the study will receive PSL 100mg bid on Day 1 and PSL 200mg bid on Day 2 and Day 3. The following procedures/assessments will be performed:

- C-SSRS for ambulatory study participants only ("Since Last Visit" version of the C-SSRS)
- Record intake of grapefruit, starfruit, or pawpaw
- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, and DBP)
- Triplicate 12-lead ECGs (shortly prior to collection of PK samples)
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)
- Blood samples (venous) for trough PK analysis (prior to PSL morning dose):
  - PSL and metabolites ([redacted] and [redacted]) levels
- Dispense PSL
- Recording of AEs/medical procedures

8.2.2 Maintenance Period

8.2.2.1 Day 4 to Day 7

Study participants will receive PSL 400mg bid and will check in to the unit on the afternoon of Day 7. The following procedures/assessments will be performed:

- C-SSRS for ambulatory study participants only ("Since Last Visit" version of the C-SSRS)
- Record intake of grapefruit, starfruit, or pawpaw
- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, and DBP)
- Triplicate 12-lead ECGs (shortly prior to collection of PK sample)
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)

- Blood samples (venous) for trough PK analysis (prior to PSL morning dose):
  - PSL and metabolites ([redacted] and [redacted]) levels
- Dispense PSL
- Recording of AEs/medical procedures

8.2.2.2 Day 8 (morning)

Study participants will receive PSL 400mg in the morning. The following procedures/assessments will be performed:

- Record intake of grapefruit, starfruit, or pawpaw
- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, and DBP)
- Triplicate 12-lead ECGs
  - Approximately 0.5h prior to PSL morning dose, and 0.5h, 1h, 2h, 3h, and 6h after the morning dose
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)
- Blood samples (venous and MITRA) for PK analysis (relative to PSL morning dose):
  - PSL and metabolites ([redacted] and [redacted]) PK profile analysis (predose [within 5 minutes of dosing], 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h [to be obtained prior to evening dose])
- Dispense PSL
- Recording of AEs/medical procedures

8.2.3 Taper Period

8.2.3.1 Day 8 (evening)

Study participants will receive PSL 200mg in the evening. The following procedures/assessments will be performed:

- Triplicate 12-lead ECGs (shortly prior to PSL evening dose)
- Dispense PSL

8.2.3.2 Day 9 to Day 12

Study participants will receive PSL 200mg bid on Day 9 and Day 10. Study participants will receive PSL 100mg bid on Day 11 and Day 12. All study participants must be confined to the unit for the entire Taper Period. The following procedures/assessments will be performed:

- Record intake of grapefruit, starfruit, or pawpaw

- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, and DBP)
- Triplicate 12-lead ECGs (shortly prior to collection of PK samples)
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)
- Blood samples (venous) for trough PK analysis (prior to PSL morning dose):
  - PSL and metabolites ([redacted] and [redacted]) levels
- Dispense PSL
- Recording of AEs/medical procedures

8.3 Safety Follow-Up Period

8.3.1 Day 13

The following procedures/assessments will be performed prior to discharge:

- C-SSRS ("Since Last Visit" version of the C-SSRS)
- Full physical examination
- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, and DBP)
- Triplicate 12-lead ECGs (shortly prior to collection of PK samples)
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)
- Blood samples (venous) for trough PK analysis:
  - PSL and metabolites ([redacted] and [redacted]) levels
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Hematology, serum chemistry, and urinalysis
- Recording of AEs/medical procedures

8.3.2 End of Study Visit

The following procedures/assessments will be performed 7 to 9 days after last dose of PSL or upon discontinuation of the study (EOS Visit):

- C-SSRS ("Since Last Visit" version of the C-SSRS)
- Full physical examination

- Prior and concomitant medications
- Vital signs (including PR, RR, SBP, DBP, and oral temperature)
- Triplicate 12-lead ECGs (prior to collection of PK samples)
- Blood samples (venous) for trough PK analysis (prior to AED morning dose):
  - MHD plasma level (only for study participants taking OXC)
  - AED trough level (for storage)
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Urine pregnancy test (for women of childbearing potential only)
  - Hematology, serum chemistry, and urinalysis
- Recording of AEs/medical procedures

8.4 Withdrawal Visit

Study participants who withdraw from the study for any reason after the first dose, but prior to Day 13, will be asked to return to the unit to complete an Early Termination Visit (7 days ± 1 day, postdose). The same assessments as for the EOS Visit (see Section 8.3.2) will be performed. Study participants who withdraw between enrollment and first dose will be followed up only at the discretion of the Investigator.

8.5 Unscheduled Visit

At the Investigator's discretion, an Unscheduled Visit may be completed at any time during the study if deemed necessary for the study participant's safety and wellbeing. The assessments to be conducted during an Unscheduled Visit will be based on the Investigator's judgement.

9 ASSESSMENT OF PHARMACOKINETIC VARIABLES

9.1 Pharmacokinetic variables

The PK variables are described in detail in Section 4.1. Calculations of PK variables will be made with Phoenix® WinNonlin® (version 6.3 or higher) using actual sampling times. The linear trapezoidal method will be used to calculate the AUC parameters. For details of PK analyses, refer to Section 12.3.1.

9.2 Pharmacokinetic sampling procedures

Study participants are requested to provide blood samples for measurement of PSL levels using the VAMS technology on the MITRA microsampling device.

9.2.1 Blood pharmacokinetic sampling scheme

Serial blood samples for PK analysis of PSL (venous and MITRA) and its metabolites ([redacted] and [redacted]; venous only) will be collected as described in Section 5.3 and Table 5-1.

The total blood volume collected for the study will not exceed 500mL per study participant.

Exact sampling times will be recorded in the eCRF.

All sample handling procedures, including the time of each sample collection, the start and stop time of centrifugation and placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail.

Time deviations from scheduled sampling times will be discussed at the Data Review Meeting.

Full details of sample handling and processing are provided in the Laboratory Manual.

The maximum deviations from scheduled sampling times considered irrelevant for PK are defined in Table 9-1.

Table 9-1: Irrelevant time deviations for PK sampling

PK blood sampling times	Deviation from scheduled time considered irrelevant
0 hours (predose)	Within 60 minutes
0.25 to 4 hours	5 minutes
6 to 12 hours	10 minutes

PK=pharmacokinetic

9.3 Shipment procedures

Details of the PK samples labelling and shipment procedures will be provided in the Laboratory Manual.

9.4 Communication plan

A communication plan dedicated to PK laboratory activities (at the least) will be established in a separate document.

9.5 Bioanalytical method

Plasma concentrations of PSL, PSL metabolites ([redacted] and [redacted]), and AEDs will be determined with validated bioanalytical methods. Blood concentrations of PSL collected by MITRA devices will be determined with a validated bioanalytical method.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation study participant 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), including any pretreatment and posttreatment periods required by the

protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

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

10.1.1.2 Serious adverse event

Once it is determined that a study participant 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 study participant and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 10.1.1.3], 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 study participant 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.)

10.1.1.2.1 Anticipated serious adverse events

The following anticipated SAEs are anticipated to occur in the epilepsy population at some frequency that is independent of drug exposure (Table 10-1)

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 10.1.2.3.

Table 10-1: Anticipated SAEs for the epilepsy population

MedDRA SOC	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.

10.1.1.3 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. No AEs of special interest have been identified for PSL to date, with the exception of potential Hy's Law cases, as described below.

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

10.1.2 Procedures for reporting and recording adverse events

The study participant 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.

10.1.2.1 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 study participant'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.

10.1.2.2 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

10.1.2.3 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 Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

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

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

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

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each study participant, and to also inform participating study participants 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.

10.1.3 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 study participant 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 10.6.1.4.

If an AE is ongoing at the end of the study for a study participant, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the study participant 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 study participant has discontinued his/her IMP.

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

10.2 Pregnancy

If an Investigator is notified that a study participant 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 Serious Adverse Event reporting information at the beginning of this protocol). The study participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The study participant should immediately stop the intake of the IMP.
- The study participant should return for an EOS Visit 7 to 9 days after the study participant has discontinued her IMP.

The Investigator must inform the study participant 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 study participant is lost to follow up and/or refuses to give information, written documentation of attempts to contact the study participant 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 study participant enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the study participant to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IEC and should be available in the Investigator site file. In case of questions about the consent

process, the Investigator may contact the UCB/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 Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

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

10.3 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.

10.4 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).

10.5 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, clinical study participants, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of 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.

10.6 Laboratory measurements

Blood and urine samples will be taken for clinical laboratory assessments at the time points specified in Table 5-1.

A urine drug screen and alcohol breath test will be performed at the Screening Visit (Day -28 to Day -2) and before study participants are admitted to the unit on Day -1. Serology will be performed at the Screening Visit to assess study participant eligibility. A serum pregnancy test

will be administered at the Screening Visit. A urine pregnancy test will be administered at Baseline and the EOS Visit.

Laboratory safety measurements will be performed after a fasting period of at least 4 hours only at the Screening Visit. Clinical laboratory parameters to be measured are presented in Table 10-2.

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

Table 10-2: Laboratory measurements

Hematology	Hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, platelets, total white blood cell count, and differential consisting of absolute counts and percentages of the following leukocyte types: neutrophils, lymphocytes, monocytes, eosinophils, and basophils
Serum chemistry	Sodium, potassium, calcium, inorganic phosphorus, fasting glucose, urea, creatinine, total bilirubin (conjugated bilirubin when total bilirubin is outside the reference range), total protein, albumin, ALT, AST, and ALP
Viral serology (only at Screening Visit)	HIV-1/2Ab, HBsAg, and HCV-Ab
Pregnancy	Serum pregnancy test at the Screening Visit
Hormone tests	Follicle-stimulating hormone (at Screening only to confirm postmenopausal status in female study participants)
Urinalysis	Specific gravity, pH, glucose, protein, blood, leukocytes, nitrite, ketones, bilirubin, urobilinogen (with dipstick) If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.
Drug screen	Amphetamines/methamphetamines, benzodiazepines, barbiturates, cocaine, cannabis, methadone, tricyclic antidepressants, and opiates

ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibodies

10.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4.3, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.6.1.1). 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 10.6.1.4).

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 6.4.3), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings.

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

Table 10-3 summarizes the approach to investigate PDILI.

Table 10-3: Required investigations and follow up for PDILI

Laboratory value		Symptoms [a] of hepatitis or hypersensitivity	Consultation requirements	Required testing	Continued evaluation
ALT or AST	Total bilirubin				
Requires immediate and permanent IMP discontinuation					
≥3xULN	<2xULN	No	Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and study participant discussed with Medical Monitor ASAP.	Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.6.1.3); recommended to occur within 24 hours at Phase 1 unit or with HCP.	Monitoring of liver chemistry values required once per week until values normalize, stabilize, or return to within baseline values. [b]
≥3xULN	NA	Yes	Hepatology consult. [c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and study participant discussed with Medical Monitor ASAP.		Monitoring of liver chemistry values required at least twice per week until values normalize, stabilize, or return to within baseline values. [b]
≥3xULN	≥2xULN [d]	NA			

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] 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.

[c] Details provided in Section 10.6.1.1. 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] If the study participant also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

10.6.1.1 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 study participant must be discussed with the Medical Monitor as soon as possible. If required, the study participant 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 10.6.1.3) and SAE report (if applicable).

10.6.1.2 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 requires permanent IMP discontinuation (see Section 6.4.3 and Table 10-3 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.

10.6.1.3 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 10-4 (laboratory measurements) and Table 10-5 (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 study participant 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 10-4: PDILI laboratory measurements

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

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

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

The following additional information is to be collected:

Table 10-5: PDILI information to be collected

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

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

10.6.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10-3. 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.

10.6.1.5 Optional hepatic investigation sample collection

If a study participant is undergoing further investigation for PDILI and has consented to retrospective genetic analysis per local regulations, the study participant's blood sample will be shipped to a secure storage facility. The blood sample will be retained in the UCB Hepatic Investigation Biobank to solely support retrospective genetic analyses associated with an adverse therapeutic response to PSL.

Genetic analyses of deoxyribonucleic acid isolated from the blood will be contracted by UCB to specialized third-party laboratories and analysis will be limited to:

- Uridine 5′-diphospho-glucuronosyltransferase loci − the loci responsible for Gilbert's syndrome (hyperbilirubinemia)
- Human leukocyte antigen (HLA) loci − for example, HLA-B5701 that has been associated with abacavir- and flucloxacillin-induced liver injury
- Absorption, distribution, metabolism, and excretion gene loci associated with abnormal PK

Genetic analysis of samples may be performed immediately, on a per-study basis, or as part of combined analyses across multiple studies belonging to the same clinical development program. As a result, samples will be retained for 15 years unless clinical development of the IMP is terminated, at which point all samples will be destroyed. The results determined using clinically approved diagnostic tests will be made available to the Investigator upon request.

Study participants may request at any time that their sample be removed from the UCB Hepatic Investigation Biobank and destroyed, though data from analyses already performed will remain on file. All samples, associated materials, and data will be kept securely by UCB and its agents. A sample destruction request should be made in writing to the Investigator who will notify the UCB Biorepository Manager (Global Exploratory Development, UCB, Slough, SL1 3WE, United Kingdom).

10.7 Other safety measurements

Other safety measurements will include physical examinations, vital signs, 12-lead ECGs, and assessment of suicidality.

If deemed necessary by the Investigator, eg, in case of a suspicious AE, the Investigator can initiate additional/unscheduled laboratory testing, vital signs, ECGs, or other assessments for safety evaluation during the study.

10.7.1 Physical examination

Full physical examinations will be performed at the time points specified in Table 5-1. Full physical examinations 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.

Height (study participant without shoes, and height rounded to the nearest 0.5cm) and body weight (study participant in underwear or light clothing, without shoes and rounded to the nearest 0.1kg) will be recorded at the Screening Visit and BMI will be derived (weight (kg)/ [height (m)]^2).

10.7.2 Vital signs

Vital signs (PR, RR, SBP, DBP, and oral temperature) will be recorded at the time points shown in Table 5-1.

For the purposes of assessing the inclusion criterion, at the Screening Visit and the Baseline Visit, BP measurements will be performed in both supine and standing positions

according to the following procedure: Measure supine BP after the study participant has been lying down for 10 minutes, then ask the study participant to stand up and record the standing BP after 1 minute and 3 minutes. At all time points after the Baseline Visit, BP will only be measured in the supine position, ie, there will be no assessment for orthostatic hypotension.

By decision of the sponsor and the Investigator, the time points specified in Table 5-1 may be modified based on preliminary safety and PK assessments from previous doses tested in the study.

10.7.3 Standard 12-lead ECG

Triplicate standard 12-lead ECGs (RR interval, PR interval, QRS interval, QT, QTcB, and QTcF) will be recorded at times specified in Table 5-1, according to the following procedure: study participant lies in a supine position for ≥5 minutes; then a 12-lead ECG will be recorded in the same position. All ECG recordings will be performed in triplicate at 2- to 3-minute intervals.

Electrocardiograms will be recorded at a speed of 25mm/s and with a calibration of 1cm/mV.

The purpose of the enhanced ECG monitoring procedures in this study is to match the observed ECG parameters with the contemporaneous plasma levels of PSL as closely as possible, at key time points during Day -1 (no exposure) and Day 8 (anticipated peak exposure). This will support an evaluation of any relationship between exposure to PSL and changes in key ECG parameters, most particularly QT intervals.

As specified in Table 5-1, a Baseline ECG series will be performed on Day -1. On this day, triplicate standard 12-lead ECGs will be performed for each of the following time points, intended to match as closely as possible the timing of the PK sampling series planned for Day 8: 0h, 30min, 1h, 2h, 3h, 6h and the pre-evening dose PK sample. On Day 8, a matching series of ECGs will be performed predose, 30min, 1h, 2h, 3h, and 6h after the morning dose of PSL, and approximately 30min before the evening dose, as close as possible to the time of the pre-evening dose PK sample. On Day 1 through Day 12, except Day 8, the triplicate standard 12-lead ECG will be performed prior to the morning dose of PSL, again timed to match as closely as possible to the time of the predose PK sample being taken. Care should be taken to record the timing of each ECG and PK sample as accurately as possible, to enable the precise evaluation of their temporal relationship.

By decision of the sponsor and the Investigator, the time points specified in Table 5-1 may be modified based on preliminary safety and PK assessments from the study.

The Investigator or designee will determine whether the results of the ECG are normal or abnormal. All important abnormalities should be reported. The original ECG tracing will be signed or initialed, and dated by the Investigator or designee, and will be retained at the clinical site as part of the Investigator's Site File. The original electronic file of all ECG tracings will be transferred to UCB on completion of the study, or earlier, if required.

10.7.4 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 study participant continuation in the

study or study participant withdrawal from the study if the study participant has a positive response to the CSSRS Question 4, should be based on the benefit/risk balance for continuation or discontinuation of study treatment in view of the individual study participant 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 study participant 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 (Investigator or designee, not site staff conducting the C-SSRS) and provided to UCB via the SAE reporting process.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

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

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

11.2 Monitoring

Monitoring of the study will be delegated by UCB to a CRO. The CRO will monitor the study to meet the CRO's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

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, 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 study participant). 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.

11.2.1 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.

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 study participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

11.2.2 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, study participant 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 11.2.1.

11.3 Data handling

11.3.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

11.3.2 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. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the electronic CRFs once and are subsequently verified if the study is performed using electronic data capture.

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

11.3.3 Study Participant Screening and Enrollment log/Study Participant Identification Code list

The study participant's screening and enrollment will be recorded in the Study Participant Screening and Enrollment Log.

The Investigator will keep a Study Participant Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each study participant.

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

11.4 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 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/investigational device and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

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

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

11.6 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 study participants enrolled have been protected, that enrolled study participants (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP/investigational device have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IEC SOPs, ICH GCP, and applicable regulatory requirements.

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

11.7 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.

12 STATISTICS

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

12.1 Definition of analysis sets

12.1.1 Enrolled Set

The Enrolled Set (ES) consists of all study participants who have signed the ICF.

12.1.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all study participants who have signed the ICF form and received IMP. Analysis of this set will be according to the treatment the study participants actually received.

All safety analyses will be performed using the FAS. All safety variables will be summarized by treatment.

12.1.3 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the FAS, consisting of those study participants who had no important protocol deviations (IPDs) affecting the PK parameters and for whom a sufficient number of samples are available to determine at least 1 PK parameter. The reasons for exclusion of study participants from the PK-PPS analysis set will be listed.

Data from study participants who experienced emesis during the course of the study might be excluded from the statistical analysis, depending on the time relative to the PK sampling and the frequency of the event.

12.2 General statistical considerations

Summary statistics will be provided for all safety and Baseline/demographic variables. The datasets will follow the UCB analysis data model (ADaM) data specifications. All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, NC, USA). The PK noncompartmental analysis (NCA) will be performed using Pharsight Phoenix WinNonlin

version 6.3 (or higher). Categorical endpoints will be summarized using number of participants, frequency, and percentages. Missing data will not be imputed. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation [SD], minimum, and maximum will be tabulated).

Baseline characteristics (gender, age, weight, height, BMI, body surface area) for the FAS will be summarized descriptively. Disease baseline characteristics will be also summarized for the FAS, including AED characteristics (name, dosage, frequency).

12.3 Planned pharmacokinetic analyses

12.3.1 Analysis of the primary pharmacokinetic variables

Pharmacokinetics will be determined using the PK-PPS.

Pharmacokinetic parameters of PSL (C_{max}, t_{max}, AUC_{τ}, and CL/F_{ss}) and metabolites ([redacted] and [redacted]; C_{max}, t_{max}, AUC_{τ}, and metabolite:parent ratio) will be estimated using NCA with Pharsight Phoenix® WinNonlin® v6.3 (or higher) software.

The individual plasma concentrations of venous PSL and its metabolites ([redacted] and [redacted]), and PK parameters of PSL and metabolites will be summarized by treatment group using descriptive statistics (number of observations [n], geometric mean, lower and upper 95% confidence intervals [CI], geometric coefficient of variation [CV], arithmetic mean, SD, CV, median, minimum and maximum value) and graphical displays.

Pharmacokinetic parameters (C_{max}, AUC_{τ}) of PSL will be compared between the 2 treatment groups (Group 1 [Inducers] vs Group 2 [Neutral {control}]) using analysis of variance (ANOVA) on the log-transformed parameters and estimation of geometric ratio of PK parameters between the 2 groups with their 90% CI will be provided.

12.3.2 Analysis of the secondary pharmacokinetic variables

The individual plasma concentrations of PSL metabolites and PK parameters of PSL metabolites will be summarized by treatment group using descriptive statistics and graphical displays. Pharmacokinetic parameters (C_{max}, AUC_{τ}) of PSL metabolites will be compared between the 2 treatment groups (Group 1 [Inducers] vs Group 2 [Neutral {control}]) using ANOVA on the log-transformed parameters and estimation of geometric ratio of PK parameters between the 2 groups with their 90% CI will be provided.

12.3.3 Analysis of the exploratory pharmacokinetic variables

The PSL concentrations and PK parameters obtained from MITRA microsampling method will be summarized as those obtained from the venous sampling method (see Section 12.3.1) and compared with those of the conventional venous sampling method using descriptive analysis (tables with summary statistics and graphs).

12.4 Planned safety analyses

12.4.1 Adverse events

All safety analyses will be performed using the study participants in the FAS.

All AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment and treatment-emergent according to the intake of PSL. A listing will be provided for the pretreatment and TEAEs.

The occurrence and incidence of AEs will be summarized by MedDRA SOC, Preferred Term, by group, and by characterization according to the intake of PSL (pretreatment or treatment-emergent). The occurrence and incidence of AEs will also be summarized by intensity and relationship to PSL. Adverse events leading to discontinuation and SAEs will also be summarized by group and by characterization according to the intake of PSL.

12.4.2 Laboratory measurements

Laboratory variables and changes from Baseline (Day -1) will be summarized at each time point by group. Shift tables from Baseline to each post-Baseline time point will be presented. Values outside the reference range will be flagged in the listings. The out-of-normal range values will be displayed.

12.4.3 Vital signs and ECGs

Vital sign variables (PR, RR, SBP, and DBP) and changes from Baseline (predose on Day 1) will be summarized at each time point by group. Frequency tables of values outside the normal ranges will be produced by treatment group and time point.

Electrocardiograms will be recorded 3 times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The 12-lead ECG parameters (RR interval, PR interval, QRS interval, QT, QTcB, and QTcF) and change from Baseline (time-matched Baseline on Day -1) will be descriptively summarized at each time point by group. Baseline per time (0h, 0.5h, 1h, 2h, 3h, 6h) at Day -1 is defined as the value of the corresponding time-matched measurements of the ECG parameters. Frequency tables of values outside the normal ranges will be produced by group and time point.

12.4.4 Assessment of suicidality

The C-SSRS data will be listed by group.

12.4.5 Physical examinations

Physical examination abnormalities will be listed by group.

12.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol that potentially could have a meaningful impact on the primary objective of the study. The criteria for identifying such protocol deviations will be defined within the relevant protocol deviation specification document, which is part of the data cleaning plan. The IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. After all data have been verified/coded/entered into a database, a data evaluation meeting will be performed. The purpose of this review will be to check all protocol deviations and the quality of the data. The review will also help guide the decision how to manage problems in the study participants' data (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.

12.6 Handling of dropouts or missing data

The methods for handling dropouts and missing data will be described in the Statistical Analysis Plan.

12.7 Planned interim analysis and data monitoring

There is no interim analysis planned for this study.

12.8 Determination of sample size

Considering the primary objective, and based on UP0002 (with PSL 400mg bid), the intersubject CV of AUC_τ was estimated to be 50% (PSL).

Using an intersubject CV of 50%, a total sample size of 28 study participants (14 study participants per group) provides approximately 92% power for the detection of a 43% decrease in AUC_τ of PSL with OXC vs without OXC (1.75-fold change: ratio of larger mean vs lower mean) at a significance level of α=0.05 (one-tailed test). Sample size computation was performed using Nquery Advisor® version 7.0.

A total of 28 adult study participants with epilepsy (14 study participants in Group 1 [Inducers] and 14 study participants in Group 2 [Neutral {control}]) are planned for enrollment in this study. This is deemed sufficient to meet the defined objectives.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

Study participant'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 study participant in both oral and written form by the Investigator (or designee). Each study participant 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 study participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The study participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each study participant must consent to direct access to his/her medical records for study-related monitoring, auditing, 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 IEC and use of the amended form.

The study participant may withdraw his/her consent to participate in the study at any time. A study participant 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 study participant, without having obtained his/her written consent to participate in the study.

13.2 Study participant identification cards

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

13.3 Independent Ethics Committees

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

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

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

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

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

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

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

13.4 Study participant privacy

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

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the study participant'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 study participant's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

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

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

14 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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16 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

17 SPONSOR DECLARATION

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

Approval Signatures

Name: up0070-protocol

Version: 1.0

Document Number: CLIN-000121011

Title: UP0070 Study Protocol

Approved Date: 12 Jun 2018

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 12-Jun-2018 08:19:36 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 12-Jun-2018 08:39:58 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 12-Jun-2018 19:00:34 GMT+0000