AN OPEN-LABEL, PARALLEL GROUP, SINGLE-CENTER STUDY TO INVESTIGATE THE PHARMACOKINETIC, SAFETY, AND TOLERABILITY PROFILES OF PADSEVONIL IN CYP2C19 GENOTYPED HEALTHY MALE JAPANESE STUDY PARTICIPANTS

PROTOCOL UP0083 AMENDMENT 1

PHASE 1

SHORT TITLE:

A pharmacokinetic, safety, and tolerability study of padsevonil in CYP2C19 genotyped healthy male Japanese study participants.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 1	22 Aug 2019	Substantial
Original Protocol	08 May 2019	Not applicable

Amendment 1 (22 Aug 2019)

Overall Rationale for the Amendment

This protocol was originally written utilizing a new Standard Operating Procedure (SOP) that contains provisions to ensure compliance with the 2017 European Regulatory Guidance on Risk Mitigation in First-in-Human and Early Clinical Trials (EMEA/CHMP/SWP/28367/07 Rev. 1). That UCB SOP recommends use of the specific study stopping rules for the highest risk early phase studies that are recommended in the EU guidance, and these are reflected in the current protocol template in use for early phase studies at UCB. However, the UCB SOP does allow for those stopping rules to be adapted to match the known risk profile of the product as it passes from early phase to late phase development, provided that such adaptation is approved by the UCB product-specific Benefit/Risk Team.

Unfortunately, in drawing up these current protocols, the first 2 finalized protocols mistakenly included the default stopping rules in Protocol Section 7.1.2. These studies are being initiated, using these stringent criteria which are not appropriate for a late stage clinical pharmacology study of padsevonil, at lower doses or achieve exposure levels anticipated to be no higher, than those explored in previous studies. Padsevonil has been administered to over 313 study participants to date, and the nature and pattern of its adverse effect profile is still evolving. In healthy volunteers, the few adverse events that have been severe in intensity have been transient, self-limiting, and reduced with repeated administration, with very few resulting in withdrawal of the individuals affected. Mitigation of more severe adverse events includes an extended titration and tapering of padsevonil dosing, which is known to improve tolerability.

Accordingly, it is deemed appropriate to replace the current, overly stringent stopping criteria which were included in the protocol template specifically to address UCB first-in-man study, a first multiple-dose study, and a healthy volunteer study where exposures will exceed those previously studied, with criteria more in keeping with the current state of knowledge of the product and its stage of development, to ensure that the maximum benefit is derived from studies needed to explore its tolerability, pharmacokinetic, pharmacodynamic and interaction profiles without any impact on subjects safety & data integrity.

Section # and Name	Description of Change	Brief Rationale
Serious Adverse Event Reporting	Email address for reporting was revised.	The contact information has changed.
Section 1.1, Synopsis, Overall design and Treatment Groups and Duration subsections	The durations of Study Periods have been clarified and also reflect the addition of new Study Day 14.	See the below rationale pertaining to the addition of Day 14.
Section 1.1, Synopsis, Overall design	Variant alleles of *4, *5, *6, *7, *8, *9, *10 and *12 have been deleted.	The frequencies of these variant alleles are deemed to be very low in Japanese.
Section 1.1, Synopsis, Overall design	Revised the duration of stay in the study center from Day -1 until the morning on Day 14.	This revision was made based on the site's assessment that from the safety point of view, the paticipants should be checked out from the hospital in the morning on Day 14, instead of the late evening on Day 13.
Section 1.3, Schedule of activities, Table 1-1	Added Day 14 to the Multiple-dose Period and required activities for this Study Day. Indicated that subjects will stay in the study center on Day 13.	See the above rationale.
Section 1.3, Schedule of activities, Table 1-1	Moved exploratory genotyping from Day -1 to Day 1. Added a footnote n to specify that the sample for exploratory genotyping is to be obtained prior to administration of PSL.	This is to prevent unnecessary blood collection.
Section 1.3, Schedule of activities, Table 1-1	Footnotes describing the timings of PK blood sampling on Day 1 and on Day 10 have been corrected.	Footnotes describing the timings of PK blood sampling on Day 1 and on Day 10 have been corrected.
Section 1.3, Schedule of activities, Table 1-1, Footnote d	Added further specification regarding the limit on total time for performing triplicate ECGs.	Augmented footnote for consistency with the text in Section 8.4.3.
Section 4.1, Overall design	The durations of Study Periods have been clarified and also reflect the addition of new Study Day 14.	See the above rationale.

Section 4.1, Overall design	Variant alleles of *4, *5, *6, *7, *8, *9, *10 and *12 have been deleted.	See the above rationale
Section 4.1, Overall design	Revised the duration of stay in the study center from Day -1 to 24 hours after the last dose to Day -1 until the morning on Day 14.	See the above rationale.
Section 6.1, Summary of treatment administered, Table 6-1	Deleted 25mg tablets in "Dosage Formulation"	Only 100mg tablets will be used as the study treatment.
Section 7.1.2	Revised the study hold criteria.	See overall rationale for the amendment.
Section 7.2, Treatment-emergent abnormal laboratory value criteria	Revised abnormal laboratory value criteria for absolute counts of eosinophils, neutrophils, and platelets in Discontinuation/withrdrawal Criterion 9.	These values were revised to conform with the standard values used by the study site
Section 8.4.3, Electrocardiograms	Revised the limit on total time for performing triplicate ECGs .	This revision was made based on the site's assessment that 9, rather than 4 minutes is a unified, realistic and manageable time.
Section 10.2, Protocol-required safety laboratory assessments, Footnote a	Revised to add that hematology, clinical chemistry, and urinalysis on Day -1 are also to be performed under fasting conditions (as for Screening).	This revision was made to conform to the general procedure followed by the study site.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24 hours)	
Fax	**Japan:** +81 3 6864 7400
Email	**Japan:** UCBJ-Safety@ucb.com

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

An open-label, parallel group, single-center study to investigate the pharmacokinetic (PK), safety, and tolerability profiles of padsevonil (PSL) in cytochrome P450 family 2 subfamily C member 19 (CYP2C19) genotyped healthy male Japanese study participants.

Short title:

A PK, safety, and tolerability study of PSL in CYP2C19 genotyped healthy male Japanese study participants.

Rationale:

Padsevonil has been demonstrated in vitro to be a time-dependent inhibitor of CYP2C19 (NCD2279, NCD2095). Limited data collected in UP0039 (PK study in Japanese and Caucasian study participants) suggested a weak effect of the CYP2C19 genotype on PSL disposition. Additionally, according to the Food and Drug Administration (FDA) draft guidance, a comparison of the PK parameters between poor metabolizers (PMs) and extensive metabolizers (EMs) can substitute for a drug-drug interaction (DDI) study with a strong inhibitor for the particular pathway such as CYP2C19 (Food and Drug Administration, 2017). It is therefore important to consider the implications of the CYP2C19 genotype on PSL clearance with the concomitant use of PSL and other drugs.

This study aims to determine the contribution of CYP2C19 in PSL metabolism. The results of the study will be used to inform on the DDI potential of PSL with CYP2C19 inhibitors and inducers as well as any dosing adjustments based on CYP2C19 genetic variations.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To investigate the PK of PSL in CYP2C19 genotyped healthy male Japanese study participants (extensive, intermediate, and poor metabolizers)	• The primary PK endpoints are the following: – PK parameters of PSL in plasma: ◦ single-dose (C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, and t_{max}) and ◦ multiple-dose ($C_{max,ss}$, AUC_{τ}, $t_{1/2}$, and $t_{max,ss}$) • The other PK endpoints are the following: – PK parameters of PSL in plasma: ◦ single-dose ($C_{max,bw}$, $AUC_{(0-t),bw}$, and $AUC_{,bw}$) and ◦ multiple-dose (CL_{ss}/F, $C_{max,ss,bw}$, and $AUC_{\tau,bw}$) – PK parameters of PSL metabolites ([redacted]) in plasma: ◦ single-dose (C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, t_{max}, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, and m/p [based on C_{max} and AUC]) and ◦ multiple-dose ($C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,ss}$, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, and m/p [based on C_{max} and AUC]) – PSL and its metabolites ([redacted]) in urine after single- and multiple-dose (A_e, f_e, CL_r) – Additional PK parameters of PSL metabolites ([redacted]) in urine (CL_{form})
Secondary	
• To evaluate the safety and tolerability of PSL in healthy male Japanese study participants	• The primary safety endpoint is the following: – Adverse events • The other safety endpoints are the following: – Vital signs (PR, RR, SBP, DBP, and body temperature) – 12-lead ECG parameters – Physical examination findings – Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)

DBP=diastolic blood pressure; ECG=electrocardiogram; m/p=metabolite to parent ratio; PK=pharmacokinetics; PR=pulse rate; PSL=padsevonil; RR=respiratory rate; SBP=systolic blood pressure

Overall design:

This is a Phase 1, open-label, parallel group, single-center study to investigate the PK, safety, and tolerability profiles of PSL in CYP2C19 genotyped healthy male Japanese study participants.

The study consists of a Screening Period, a Single-dose Period, a Multiple-dose Period, and a Safety Follow-up (SFU) Visit. The maximum total duration of the study is 49 days for each study participant, including the Screening Period (up to 28 days), the Single-dose Period (6 days, including Check-in on Study Day -1 and PSL single-dosing on Study Day 1 to Study Day 5, inclusive), the Multiple-dose Period (9 days, including PSL dosing on Study Day 6 to Study Day 12, inclusive), and the SFU Visit (maximum of 8 days after the last dose of PSL on Study Day 12).

The study participants will be examined for CYP2C19 genotyping (variant alleles: *2, *3, and *17) during the Screening Period and grouped as follows:

- Extensive metabolizers (*1/*1),
- Intermediate metabolizers (*1/*2, *1/*3),
- Poor metabolizers (*2/*2, *2/*3, *3/*3).

Other metabolizers who have the variant allele of *17 will be excluded from the study. Study participants will not be genotyped, if rescreened.

Study participants who meet all of the inclusion and none of the exclusion criteria will check into the study center on Day -1 (prior to the single dose [SD]). A SD of PSL 200mg will be administered in the morning on Day 1 of the Single-dose Period. During the Multiple-dose Period, PSL will be administered on the following dosage schedule:

- PSL 100mg twice a day (BID) on Day 6.
- PSL 200mg BID from Day 7 to Day 9.
- PSL 200mg in the morning on Day 10; PSL 100mg in the evening on Day 10.
- PSL 100mg BID from Day 11 to Day 12.

Padsevonil will be administered with 240mL water 30 minutes after a completion of a light meal for the morning dose and 30 minutes after a completion of a standard meal for the evening dose. During the Single-dose and Multiple-dose Periods, study participants will stay in the study center from the afternoon on Day -1 (prior to the SD) until the morning on Day 14.

Study participants will undergo serial conventional venous blood and urine sampling to measure plasma and urine concentrations of PSL and its metabolites as well as safety monitoring.

Number of participants:

A total of 39 study participants (13 study participants per CYP2C19 genotype group) will be enrolled. If more than 2 study participants dropout in each group, additional study participants will be recruited at the discretion of the Investigator and Sponsor.

Treatment groups and duration:

The maximum total duration of the study is 49 days for each study participant, including the Screening Period (up to 28 days), the Single-dose Period (6 days, including Check-in on Study Day -1 and PSL single-dosing on Study Day 1 to Study Day 5, inclusive), the Multiple-dose Period (9 days, including PSL dosing on Study Day 6 to Study Day 12, inclusive), and the SFU Visit (maximum of 8 days after the last dose of PSL on Study Day 12).

1.2 Schema

Not applicable.

1.3 Schedule of activities

The schedule of activities is provided in Table 1-1.

Table 1-1: Schedule of activities

Study Period	Screening Period (28 days)	Single-dose Period						Multiple-dose Period									SFU Or Withdrawal Visit (maximum of 8 days after the last dose) [a]
Study Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Informed consent	X																
Inclusion/exclusion	X		X														
Body weight and height	X																
CYP2C19 genotyping	X																
Exploratory genotyping			X^n														
Demographics, habits, lifestyle	X																
Medical/surgical history	X																
Concomitant medication/medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X	X														X	X
Psychiatric and mental status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X								X					X		X
Drug screen, ethanol breath test	X	X															
Serology (HBV, HCV, HIV, syphilis)	X																
Clinical laboratory tests	X	X					X								X		X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Table 1-1: Schedule of activities

Study Period	Screening Period (28 days)	Single-dose Period						Multiple-dose Period										SFU Or Withdrawal Visit (maximum of 8 days after the last dose) [a]
12-lead ECG[d]	X		X	X				X	X	X	X	X	X	X	X			X
PSL administration			X[e]					X[f]	X[g]	X[g]	X[g]	X[h]	X[i]	X[i]				
PK blood sampling			X[j]	X[j]	X[j]							X[k]						
PK urine sampling			X[l]	X[l]	X[l]	X[l]	X[l]					X[m]						
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stay in study center		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP2C19=cytochrome P450 family 2 subfamily C; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; PSL=padsevonil; SFU=Safety Follow-up Visit

[a] The Safety Follow-up Visit will be performed 7 days (±1 day) after the last administration of PSL. Idem for the Withdrawal Visit, if applicable.

[b] A complete physical examination will be conducted at Screening and SFU. A brief physical examination will be conducted at all other visits, including at discharge.

[c] On dosing days, vital signs will be performed predose and 3 hours postdose. Blood pressure measurements will be performed in both supine and standing positions for orthostatic measurement at Screening (supine BP after the study participant has been lying down for 5 minutes and then standing BP after 1 minute and 3 minutes) and in a supine position for routine BP measurements at all assessments.

[d] 12-lead ECG will be performed after a rest of ≥5 minutes at Screening and at predose, 24 hours postdose, and at the SFU Visit. All ECG recordings will be performed in triplicate but no more than 2 to 3 minutes apart. The full set of triplicates should be completed in less than 9 minutes.

[e] PSL 200mg will be administered in the morning on Day 1 during the Single-dose Period.

[f] PSL 100mg will be administered in the morning and evening on Day 6 during the Multiple-dose Period.

[g] PSL 200mg will be administered in the morning and evening from Day 7 to Day 9 during the Multiple-dose Period.

[h] PSL 200mg and 100mg will be administered in the morning and evening, respectively, on Day 10 during the Multiple-dose Period.

[i] PSL 100mg will be administered in the morning and evening from Day 11 to Day 12 during the Multiple-dose Period.

[j] Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose.

[k] Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the morning dose.

[l] Predose and 0 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 72 hours, and 72 to 96 hours postdose.

[m] 0 to 12 hours after the morning dose.

[n] Predose.

2 INTRODUCTION

2.1 Study rationale

Preclinical investigations (NCD2194) have shown that PSL is mainly metabolized by CYP3A4 with a minor contribution from CYP2C19. The clinical DDI interaction with carbamazepine, a potent CYP3A4 inducer (UP0002) confirmed the major contribution of CYP3A4 to PSL clearance as the exposure of PSL was reduced by approximately 80% when coadministered with carbamazepine. The contribution of CYP3A4 to PSL clearance was further confirmed in the DDI clinical study with erythromycin 500mg BID, a moderate CYP3A4 inhibitor (UP0057) as the exposure of PSL was increased approximately 2-fold with concomitant administration of erythromycin.

Padsevonil has been demonstrated in vitro to be a time-dependent inhibitor of CYP2C19 (NCD2279, NCD2095). This has been confirmed in the cocktail DDI clinical study (UP0013) where PSL showed a moderate increase in the exposure of omeprazole, a CYP2C19 probe substrate. Padsevonil also demonstrated time-dependent PK with decreased clearance following repeated administration at a dose of 100mg BID and higher. This is most likely due to autoinhibition of the CYP2C19 pathway involved in PSL metabolism.

Limited data collected in UP0039 (PK study in Japanese and Caucasian study participants) suggested a weak effect of the CYP2C19 genotype on PSL disposition. This effect is more pronounced after a SD compared with repeated dosing, consistent with autoinhibition of CYP2C19.

As a consequence of the potential contribution of CYP2C19 in PSL clearance, strong inhibitors and inducers of CYP2C19 are excluded from global Phase 2b and Phase 3 studies.

According to the FDA draft guidance, a comparison of the PK parameters between PMs and EMs can substitute for a DDI study with a strong inhibitor for the particular pathway such as CYP2C19 (Food and Drug Administration, DRAFT GUIDANCE, 2017). It is therefore important to consider the implications of the CYP2C19 genotype on PSL clearance with the concomitant use of PSL and other drugs.

The goal of UP0083 is to determine the contribution of CYP2C19 in PSL metabolism. The results of the study will be used to inform on the DDI potential of PSL with CYP2C19 inhibitors and inducers as well as any dosing adjustments based on CYP2C19 genetic variations.

2.2 Background

More than 50 million people worldwide suffer from epilepsy (World Health Organization, 2018). An imbalance between excitatory and inhibitory neurotransmission is widely recognized as a key factor leading to epilepsy. Consequently, drugs currently used in the treatment of epilepsy aim to restore this balance. In fact, most of the current antiepileptic drugs (AEDs) modulate neuronal transmission by either blocking voltage-gated sodium channels or acting on inhibitory/excitatory receptors located at the postsynaptic level.

The gamma-aminobutyric acid type a receptor alpha1 subunit (GABAA) receptor mediates the bulk of inhibitory neurotransmissions in the brain. Allosteric modulation of inhibitory GABAA receptors by the central benzodiazepine receptor (cBZR) site offers robust protection against seizures (Riss et al, 2008). However, their clinical use as AEDs is limited due to an unfavorable

side effect profile (eg, drowsiness, ataxia, amnesia, paradoxical aggression), as well as the development of tolerance to anticonvulsant effects.

Compounds binding to SV2A proteins on synaptic vesicles are characterized by broad-spectrum efficacy against both generalized and partial seizures in preclinical models, and this protective activity strongly correlates with their binding affinity (Kaminski et al, 2008). The function of SV2B and SV2C subtypes is not well established, but they share a high degree of sequence homology to SV2A and localization within synaptic vesicles (Wan et al, 2010; Janz and Südhof, 1999). Levetiracetam (LEV), exemplifying a SV2A related mechanism of action, displays prominent clinical efficacy in patients with different forms of epilepsy (Klitgaard and Verdru, 2007).

Compounds with dual activity at SV2A and GABAA receptors are expected to have superior efficacy to those drugs working through only one of these mechanisms. Preclinical data in animal models of epilepsy support this assumption with compelling synergistic interaction observed between LEV and AEDs with GABAergic mechanisms of action (Kaminski et al, 2009). This synergistic interaction was particularly pronounced when combinations of LEV and benzodiazepines were tested and a significant increase in anticonvulsant potency of these drugs was observed associated with a higher therapeutic index.

Padsevonil is a novel chemical entity with selective affinity for both presynaptic SV2 proteins and postsynaptic cBZR sites on the GABAA receptor. At presynaptic sites, PSL binds with high affinity to all 3 subtypes of the SV2 protein (ie, SV2A, SV2B, and SV2C), and with moderate affinity to postsynaptic cBZR sites. Pharmacological results obtained in rodent models of either partial or generalized seizures in humans show that PSL provides potent and efficacious seizure suppression, suggesting a broad-spectrum profile. Furthermore, PSL revealed potent and efficacious seizure suppression in models of drug-refractory epilepsy, suggesting superior efficacy against seizures refractory to currently used AEDs. Specifically, in the rat amygdala kindling model, a model of refractory focal epilepsy, PSL was the only compound that produced seizure freedom at doses that can be administered in humans. Valproate, brivaracetam, clonazepam, diazepam, and phenobarbital only produced seizure freedom at plasma exposures that exceeded the maximum human exposures multiple times over. Padsevonil is not associated with loss of anticonvulsant efficacy after repeated administration in mice, suggesting reduced potential for the development of tolerance. Because of its unique properties, PSL is currently being proposed as adjunctive treatment for nondrug-resistant focal seizures in patients with epilepsy.

2.3 Benefit/risk assessment

Overall, the clinical pharmacology and clinical studies in drug-resistant epilepsy demonstrated the adverse event (AE) profile of PSL is generally consistent with the pharmacological activity of the product, and as expected in the context of early dose escalation studies in healthy study participants and patients with epilepsy. The safety findings to date suggest that the AEs experienced by study participants receiving single and repeated doses of PSL are limited principally to central nervous system effects. 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.

Reported acute psychiatric serious adverse events (SAEs) are consistent with AEs of other AEDs, including SV2A ligands. Events were transient, acute, and required admission to

psychiatric care and medical treatment. The events in healthy study participants (n=2) occurred early after initiation or cessation of PSL which was done without titration or tapering. The psychotic effect in an epilepsy study participant (EP0069) emerged after dramatic improvement in seizure control and electroencephalogram activity a few weeks after the start of PSL, suggesting a "forced normalization" (Clemens, 2005, Loganathan et al, 2015). Dose reduction of PSL and medical treatment resulted in complete resolution of psychosis within days, as the treatment with PSL continued. The occurrence of acute psychiatric SAEs in these three study participants administered PSL highlights the need to consider the possibility of significant psychiatric AEs and to maintain vigilance for such effects. The mitigation plan for acute psychiatric SAEs involves gradual titration and taper, which are known to improve tolerability of AEDs and monitoring for psychiatric and mental status changes.

Despite the occurrence of several electrocardiogram (ECG) findings (including different types of ectopy) both in healthy study participants and study participants with epilepsy, an independent expert cardiologist reviewed data from Phase 1 and Phase 2 and determined that none of these findings were assessed as being likely to be related to PSL. No clinically significant echocardiographic findings (only minor/trace or Grade 1 findings) have been observed in studies EP0069 and EP0073 and all echocardiograms were assessed as normal. There are currently no data to suggest that the drug has an AE on cardiovascular function other than a minimal lowering effect on blood pressure (BP). The degrees of reduction seen in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are consistent with the GABAA targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use. As a precaution, and in view of the nonclinical histopathological cardiac findings, echocardiogram screening of study participants at Baseline and ongoing echocardiogram monitoring during treatment and posttreatment have been implemented in the studies that have a >3-week treatment duration. To date, no clinically significant echocardiogram findings (only minor/trace or Grade 1 findings) have been observed.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PSL may be found in the Investigator's Brochure (IB). The current IB reflects the safety profile of PSL as it is known and may change with the accumulation of additional data.

The healthy study participants included in this study will receive no medical benefit from participation. The risks from taking part in the study will be minimized through the selection of appropriate dose levels, selection of appropriate study participants defined by the inclusion/exclusion criteria, and safety monitoring.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for this study are presented in Table 3-1.

Table 3-1: Study objectives and endpoints

Objectives	Endpoints
Primary	
• To investigate the PK of PSL in CYP2C19 genotyped healthy male Japanese study participants (extensive, intermediate, and poor metabolizers)	• The primary PK endpoints are the following: – PK parameters of PSL in plasma: ◦ single-dose (C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, and t_{max}) and ◦ multiple-dose ($C_{max,ss}$, AUC_{τ}, $t_{1/2}$, and $t_{max,ss}$) • The other PK endpoints are the following: – PK parameters of PSL in plasma: ◦ single-dose ($C_{max,bw}$, $AUC_{(0-t),bw}$, and $AUC_{,bw}$) and ◦ multiple-dose (CL_{ss}/F, $C_{max,ss,bw}$, and $AUC_{\tau,bw}$) – PK parameters of PSL metabolites ([redacted]) in plasma: ◦ single-dose (C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, t_{max}, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, and m/p [based on C_{max} and AUC]) and ◦ multiple-dose ($C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,ss}$, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, and m/p [based on C_{max} and AUC]) – PSL and its metabolites ([redacted]) in urine after single- and multiple-dose (A_e, f_e, CL_r) – Additional PK parameters of PSL metabolites ([redacted]) in urine (CL_{form})
Secondary	
• To evaluate the safety and tolerability of PSL in healthy male Japanese study participants	• The primary safety endpoint is the following: – Adverse events • The other safety endpoints are the following: – Vital signs (PR, RR, SBP, DBP, and body temperature) – 12-lead ECG parameters – Physical examination findings – Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)

DBP=diastolic blood pressure; ECG=electrocardiogram; m/p=metabolite to parent ratio; PK=pharmacokinetics; PR=pulse rate; PSL=padsevonil; RR=respiratory rate; SBP=systolic blood pressure

4 STUDY DESIGN

4.1 Overall design

This is a Phase 1, open-label, parallel group, single-center study to investigate the PK, safety, and tolerability profiles of PSL in CYP2C19 genotyped healthy male Japanese study participants.

A study participant who provides written informed consent will be screened within 28 days before the Single-dose Period.

The study consists of a Screening Period, a Single-dose Period, a Multiple-dose Period, and a SFU Visit. The maximum total duration of the study is 49 days for each study participant, including the Screening Period (up to 28 days), the Single-dose Period (6 days, including Check-in on Study Day -1 and PSL single-dosing on Study Day 1 to Study Day 5, inclusive), the Multiple-dose Period (9 days, including PSL dosing on Study Day 6 to Study Day 12, inclusive), and the SFU Visit (maximum of 8 days after the last dose of PSL on Study Day 12).

The study participants will be examined for CYP2C19 genotyping (variant alleles: *2, *3, and *17) during the Screening Period and grouped as follows:

- Extensive metabolizers (*1/*1),
- Intermediate metabolizers (*1/*2, *1/*3),
- Poor metabolizers (*2/*2, *2/*3, *3/*3).

Other metabolizers who have the variant allele of *17 will be excluded from the study. Study participants will not be genotyped, if rescreened.

A sufficient number of study participants will be screened to ensure that 13 study participants are included in each group.

Study participants who meet all of the inclusion and none of the exclusion criteria will check into the study center on Day -1 (prior to the SD). A SD of PSL 200mg will be administered in the morning on Day 1 of the Single-dose Period. During the Multiple-dose Period, PSL will be administered on the following dosage schedule:

- PSL 100mg BID on Day 6.
- PSL 200mg BID from Day 7 to Day 9.
- PSL 200mg in the morning on Day 10; PSL 100mg in the evening on Day 10.
- PSL 100mg BID from Day 11 to Day 12.

Padsevonil will be administered with 240mL water 30 minutes in after a completion of a light meal for the morning dose and 30 minutes in after a completion of a standard meal for the evening dose. During the Single-dose and Multiple-dose Periods, study participants will stay in the study center from the afternoon on Day -1 (prior to the SD) until the morning on Day 14.

Study participants will undergo serial conventional venous blood and urine sampling to measure plasma and urine concentrations of PSL and its metabolites as well as safety monitoring.

Study participants will return to the study center for the SFU Visit 7 (±1) days after the final dose of PSL.

4.2 Scientific rationale for study design

Padsevonil has been demonstrated in vitro to be a time-dependent inhibitor of CYP2C19 (NCD2279, NCD2095). Limited data collected in UP0039 (PK study in Japanese and Caucasian study participants) suggested a weak effect of the CYP2C19 genotype on PSL disposition. This effect is more pronounced after a SD compared with repeated dosing, consistent with autoinhibition of CYP2C19.

As a consequence of the potential contribution of CYP2C19 in PSL clearance, strong inhibitors and inducers of CYP2C19 are excluded from global Phase 2b and Phase 3 studies.

According to the FDA draft guidance, a comparison of the PK parameters between PMs and EMs can substitute for a DDI study with a strong inhibitor for the particular pathway such as CYP2C19. Healthy male Japanese adults were chosen as a study population because the frequency of CYP2C19 PMs is estimated to be approximately 20% in the Japanese population whereas in the Caucasian population it is 1% to 3%.

4.3 Justification for dose

The dosages of PSL for this study will be 200mg SD, 200mg BID, and 100mg BID for titration and tapering (Section 4.1). The 200mg SD was used to evaluate the safety, tolerability, and PK of PSL in healthy Japanese and Caucasian study participants in UP0039. The 200mg BID is being evaluated in global Phase 2 and Phase 3 studies as a potential dose for registration and approval. In addition, while this dose is lower than the maximum tolerated dose (MTD; 400mg BID), it is considered adequate for the purposes of this study while not exposing healthy study participants to the MTD.

4.4 End of study definition

A study participant is considered to have completed the study if he has completed all periods of the study including the last scheduled procedure shown in the Schedule of activities (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of activities (Section 1.3) for the last study participant in the study.

The maximum study duration per study participant is 49 days, including up to 28 days for Screening and 21 days on study (ie, from Day -1 through the SFU Visit).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Study participants are eligible to be included in the study only if all of the following criteria apply:

Age:

1. The study participant must be 20 to 55 years of age inclusive, at the time of signing the informed consent.

Type of study participant and disease characteristics:

2. The study participant is overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

   Note: Study participant has clinical laboratory test results within the local reference ranges or values that are considered as not clinically relevant by the Investigator and approved by the UCB Study Physician. Lab 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 will be allowed in the study.

3. The study participant is of Japanese descent as evidenced by appearance and verbal confirmation of familial heritage (a study participant has all 4 Japanese grandparents born in Japan).

Weight:

4. The study participant has a body weight ≥50kg and body mass index within the range [18 to 30] kg/m^2 (inclusive).

Sex:

5. The study participant is male.

   A male study participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the Treatment Period and for ≥7 days after the last dose of study medication and refrain from donating sperm during this period.

Informed consent:

6. The study participant is capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF).
7. The study participant must be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator, and is capable of communicating satisfactorily with the Investigator.

5.2 Exclusion criteria

Study participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. The study participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study, such as 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.
2. The study participant has a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders, capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
3. The study participant has history of chronic alcohol or drug abuse within the previous 6 months.
4. The study participant has a positive predrug/alcohol screen (to include at a minimum amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines).

   Note: A study participant with a positive finding on the alcohol and/or drug screen may still be enrolled at the discretion of the Investigator if a plausible clinical explanation exists (eg, prior or concomitant medication use).
5. The study participant has a known hypersensitivity to any components of the study medication or comparative drugs (and/or an investigational device) as stated in this protocol.
6. The study participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
7. The study participant has abnormal blood pressure.

   Note: This includes both the routine and orthostatic hypotension BP assessments. For routine BP, the study participant must have BP and pulse rate within normal range in the supine position after 5 minutes of rest (SBP: 90mmHg to 145mmHg; DBP: 40mmHg to 95mmHg; and pulse rate: 40bpm to 100bpm). Any values marginally (ie, no more than 5mmHg) outside the normal range but considered not clinically significant by the Investigator would be allowed. In case of an out of range result, 1 repeat will be allowed. If the readings are out of range again, the study participant will not be included.
8. The study participant has lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

Suicidality

9. The 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 Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Prior/Concomitant therapy

10. The study participant has past or intended use of over-the-counter or prescription medication including herbal medications within 2 weeks or 5 half-lives prior to dosing. Specific medications listed in Section 6.5.1 may be allowed.
11. The study participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin, etc.) within 2 months prior to dosing. In case of uncertainty, the Medical Monitor should be consulted.

Prior/Concurrent clinical study experience

12. The study participant has previously received PSL in this or any another study.
13. The study participant has participated in another study of an investigational medicinal product (IMP) (and/or an investigational device) within the previous 30 days prior to Screening (or within 5 half-lives, whichever is longer) or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

14. The study participant has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0x upper limit of normal (ULN).
15. The study participant has bilirubin >1.0xULN (isolated bilirubin >1.0xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. The study participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

    Note: Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.
17. The 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 study participants 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.

    NOTE A: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.

    NOTE B: The specific formula used to determine eligibility and discontinuation for an individual study participant should be determined prior to initiation of the study. In other

words, several different formulas cannot be used to calculate the QTc for an individual study participant and then the lowest QTc value used to include or discontinue the study participant.

18. The study participant has presence of hepatitis B surface antigen at Screening or within 3 months prior to dosing.
19. The study participant has positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention.

    NOTE: Study participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
20. The study participant has positive human immunodeficiency virus antibody test or syphilis at Screening or within 3 months prior to dosing.

Other exclusions

21. The study participant has made a blood or plasma donation or has had a comparable blood loss (>450mL) within the last 30 days prior to Screening. Blood donation during the study is not permitted.
22. The study participant has a consumption of 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).
23. The study participant smokes more than 5 cigarettes per day (or equivalent) or has done so within 6 months prior to Screening.
24. The study participant ingests grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before each administration of study medication. If this is the case at the start of the study, study participants may be rescreened.
25. The study participant has a diet that deviates notably from the “normal” amounts of protein, carbohydrate, and fat, as judged by the Investigator.
26. The study participant has undergone sudden and/or extreme changes in exercise levels for 2 weeks prior to Screening Visit.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- The study participant must refrain from consumption of grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) from 3 days before the start of study medication until after the final dose.
- All morning doses will be administered in the ante meridiem and all evening doses will be administered in the post meridiem.
- Study participants will complete a light meal 30 minutes prior to each morning dose of PSL and a standard meal 30 minutes prior to each evening dose of PSL. On days when PK

assessments will be taken, study participants will complete a standardized meal (same macronutrient will be administered for minimizing covariates) in the afternoon and evening.

- PSL will be administered orally with 240mL water. Between 1 hour predose and 2 hours postdose, the total intake of beverages should be limited to 100mL. Water will be available ad libitum except for between 1 hour before and 2 hours after dosing.

5.3.2 Caffeine, alcohol, and tobacco

- During each dosing session, study participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK sample.
- During each dosing session, study participants will abstain from alcohol for 24 hours before the start of dosing until leaving the study center.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3 Activity

- Study participants will abstain from strenuous exercise from 3 days before each blood collection for clinical laboratory tests. Study participants may participate in light recreational activities during the study (eg, watching television, reading).

5.4 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure study participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1 Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (at the discretion of the Investigator). Study participants may be rescreened under conditions including but not limited to the following:

- Study participant ingests grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before each administration of study medication.
- If a study participant does meet the exclusion criteria at Screening or on Day -1 due to an out-of-range laboratory result or a minor illness, he can be rescreened once at the discretion of the Investigator.
- Study participants may be included if the repeat values for the laboratory screening criteria are within normal ranges and/or if repeat values show normalization of the out-of-range safety laboratory values, and/or after the study participant makes a complete recovery from the mild illness and if all other screening criteria are met.
- Study participant has a positive drug test for substances of abuse.

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

In any case of uncertainty, this should be discussed with the Medical Monitor.

Rescreened study participants will be assigned the same study participant number as for the initial Screening.

6 STUDY TREATMENT

Study treatment or study medication is defined as any investigational treatment intended to be administered to a study participant according to the study protocol.

6.1 Treatment administered

A summary of the treatment administered is provided in Table 6-1.

Table 6-1: Summary of treatment administered

Study Treatment Name:	**PSL**
Dosage formulation:	100mg tablets
Unit dose strength(s)/Dosage level(s):	100mg, 100mg BID, 200mg, 200mg BID
Route of administration:	Oral
Dosing instructions:	Padsevonil will be administered with 240mL of water. The use of beverages between 1 hour predose and 2 hours postdose should be limited to a maximum of 100mL (in order to keep groups comparable with respect to period of dosing). Study participants will complete a light meal 30 minutes prior to each morning dose and a standard meal 30 minutes prior to the evening dose. Single-dose Period: PSL 200mg SD in the morning on Day 1. Multiple-dose Period: PSL 100mg BID on Day 6, 200mg BID from Day 7 to Day 9, 200mg SD ante meridiem on Day 10, 100mg SD post meridiem on Day 10, and 100mg BID from Day 11 to Day 12. Treatments will be administered in an open-label fashion. Study participants will be dosed in an upright position and will remain semi-recumbent until 4 hours afterwards.

Table 6-1: Summary of treatment administered

Study Treatment Name:	PSL
Packaging and labeling:	Padsevonil tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.
Manufacturer:	UCB

BID=twice per day; min=minute; PSL=padsevonil; SD=single dose

6.2 Preparation, handling, storage, and accountability requirements

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.

Only study participants enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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 study medication following the instructions on the label.

Further guidance and information for the final disposition of unused study medication are provided in the 'UP0083 IMP Handling Manual' (IP Instruction for Handling).

6.2.1 Drug accountability

A Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication 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 study medication 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 study medication 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 study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedure 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.

6.3 Measures to minimize bias

This is an open-label study.

At Screening, each study participant will be assigned a unique 5-digit study participant number from a range of numbers supplied by UCB Clinical Data Operations, Technology, and Standards.

6.4 Treatment compliance

Study participant compliance will be ensured by the administration of study medication by designated site personnel. Drug accountability must be recorded on the Drug Accountability form.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medication is permitted during the study:

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

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- With the exception of permitted concomitant treatments listed in Section 6.5.1, all prescription or nonprescription medicines are prohibited within 2 weeks or 5 half-lives whichever is longer of the respective drug prior to first administration of PSL and during the clinical part of the study unless required to treat an AE. This includes all over-the-counter remedies, vitamins and herbal, and dietary supplements (including St. John's Wort).
  - Hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin, etc.) should not be used within 2 months prior to dosing. In case of uncertainty, the Medical Monitor should be consulted.
- Drugs of unknown half-lives are prohibited within 2 weeks before administration of PSL and during the clinical part of the study, unless required to treat an AE.

If a study participant needs or takes any prohibited medication, the Investigator will (where possible) discuss with the Sponsor Study Physician and a decision will be made whether the study participant can continue in the study or must be withdrawn.

6.5.3 Rescue medication

Not applicable.

6.6 Dose modification

No PSL dose modifications are permitted during the study for an individual study participant unless necessary to protect study participant's safety or well-being.

6.7 Treatment after the end of the study

There are no plans for continued study participant care or treatment after the end of the study.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

Study medication will be stopped if the study participant develops a medical condition (or laboratory abnormality or ECG change) that, in the opinion of the Investigator, compromises the study participant's ability to participate or compromises the study participant's safety.

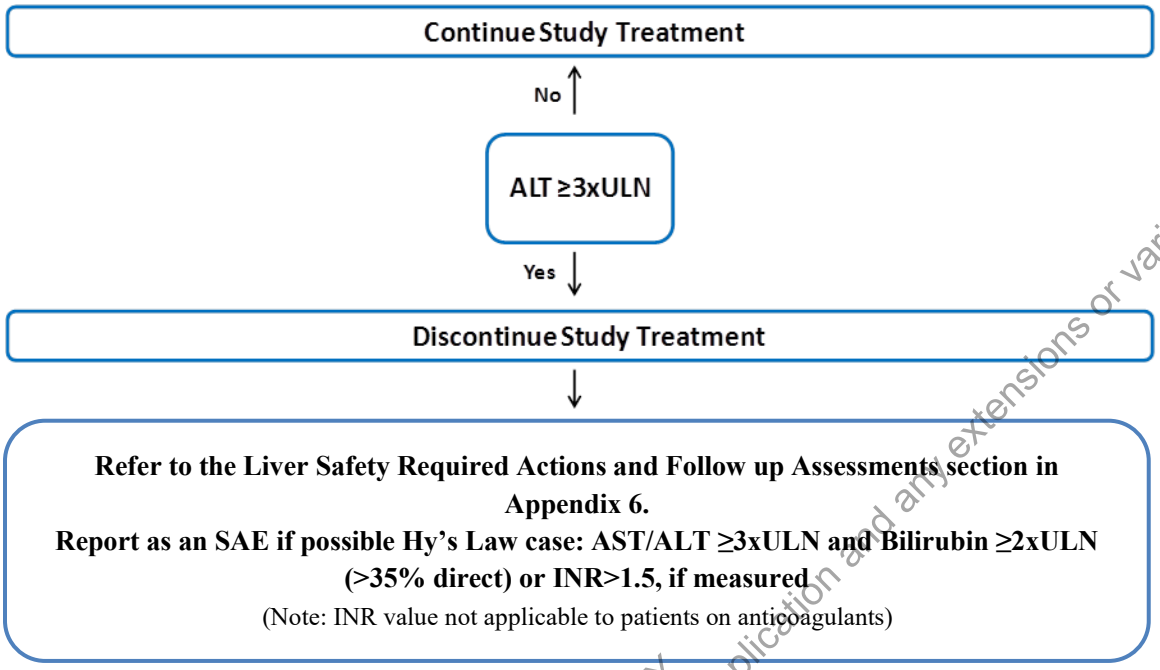
In all cases the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB Study Physician. If a study participant discontinues study medication, no restart will be allowed.

7.1.1 Liver chemistry stopping criteria

Discontinuation of study medication for abnormal liver function should be considered by the Investigator when a study participant meets 1 of the conditions outlined in Figure 7-1 or if the Investigator believes that it is in best interest of the study participant.

Study medication will be discontinued immediately and permanently for a study participant if liver chemistry stopping criteria are met.

Figure 7-1: Liver chemistry stopping algorithm



ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Specific assessments and follow up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 6 (Section 10.6).

7.1.2 Criteria for study hold/stopping due to adverse events

In recognition of the advanced status of the development program for PSL, the following study hold/stopping rules will apply to this study.

In the event that either or both of the following criteria are met, a safety review will be immediately initiated:

- The occurrence of a serious adverse reaction (SAR) (ie, an SAE considered at least possibly related to the study medication) in 2 study participants, where those SARs occur in the same body system.
- The occurrence of a severe nonserious adverse reaction (ie, severe nonserious AEs considered at least possibly related to the study medication) in 3 study participants, where those severe adverse reactions:
  - Occur in the same body system, and
  - Lead to withdrawal of the affected participant

The safety review will be conducted by an internal, study-specific Safety Monitoring Committee comprised of the Investigator and appropriate members of the UCB Study Team (such as the Study Physician, Safety Physician, Clinical Project Manager, and Clinical Pharmacologist), as quickly as possible, to review the available data and determine whether it is appropriate to continue dosing at the next scheduled dosing point. This will take the form of a risk/benefit

evaluation from the perspective of the individual study participants. In making this evaluation, account will be taken of the potential risks of sudden discontinuation of study medication, particularly in participants who may be taking higher dose levels, and whether or not a tapering period, and its duration/speed, should be undertaken.

The Safety Monitoring Committee will also decide whether it is appropriate to continue the study with or without dose adaptations, additional safety assessments, or other changes in design. If such changes are deemed necessary to protect the wellbeing of participants, further dosing in the study will be suspended while a substantial amendment is submitted to the Country(ies) Health Authority and Research Ethics Committee(s), and the study will not restart until that amendment has been approved.

If the Safety Monitoring Committee cannot be convened before the next scheduled dosing point, the Investigator will make an independent evaluation as to whether it is appropriate to continue dosing pending the review.

Detailed procedures for reporting SAEs and other safety events which may meet study hold/stopping criteria, are provided in Appendix 3 (Section 10.3).

7.1.3 Temporary discontinuation

If a study participant discontinues study medication, no restart will be allowed.

7.2 Participant discontinuation/withdrawal from the study

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

A study participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of activities (Section 1.3) for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.

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

1. The study participant develops a clinically relevant medical condition (physical or psychiatric) that, in the opinion of the Investigator, jeopardizes or compromises the study participant's ability to participate in the study or made it unsafe to continue.
2. The study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. The study participant takes prohibited concomitant medications as defined in this protocol.
4. The study participant withdraws his consent.
5. The Sponsor or a regulatory agency requests withdrawal of the study participant.

6. The study participant has changes in the ECG that are regarded as clinically significant and/or that worsen over time. An ECG shows an absolute value for QTcB or QTcF ≥500ms or ≥60ms above Baseline.
7. The study participant develops a second- or third-degree atrioventricular block or another clinically relevant change in ECG as determined by the Investigator.
8. The study participant has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The 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 PSL.
   - The study participant 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.
9. The study participant is suspected of having a serious multiorgan hypersensitivity reaction. Serious suspected multiorgan hypersensitivity cases may be identified and reported to the Sponsor by the Investigator using the following algorithm:
   - An AE or laboratory value (as defined below) suggestive of internal organ involvement including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.
   - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
     - Eosinophils percentage ≥10%.
     - Eosinophils absolute ≥$5.0\times10^2/\mu L$.
     - Neutrophils absolute <$15.0\times10^2/\mu L$.
     - Platelets absolute ≤$10.0\times10^4/\mu L$.

Withdrawn study participants should follow the taper schedule, if possible, unless faster discontinuation is considered necessary in the medical judgment of the Investigator. Investigators should attempt to obtain information on study participants in the case of withdrawal.

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

7.3 Lost to follow up

A study participant will be considered lost to follow up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a study participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible and counsel the study participant on the importance of maintaining the assigned

visit schedule and ascertain whether or not the study participant wishes to and/or should continue in the study.

- Before a study participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the study participant (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 must document the primary reason for withdrawal.

Should the study participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow up documented in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of activities (Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the study participant should continue or discontinue study medication.

Adherence to the study design requirements, including those specified in the Schedule of activities (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential study participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all study participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the study participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of activities (Section 1.3).

The maximum amount of blood collected from each study participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL per study participant. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Not applicable.

8.2 Pharmacokinetics

Whole blood samples (conventional venous blood sampling) will be collected for measurement of plasma concentrations of PSL and its metabolites and urine samples will also be collected for measurement of urine concentrations of PSL and its metabolites as specified in the Schedule of activities (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment.

Instructions and additional details regarding PK sampling are provided in the Laboratory Manual.

8.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.4 Safety assessments

The safety and tolerability of single and multiple doses of PSL will be monitored by evaluation of AEs, clinical laboratory test results, vital signs (pulse rate, respiratory rate, SBP, DBP, and body temperature), 12-lead ECG parameters, psychiatric and mental status, physical examination findings, and suicidal risk monitoring. Planned time points for all safety assessments are provided in the Schedule of activities (Section 1.3).

8.4.1 Physical examination

Physical examinations will be performed at Screening and at the time points specified in Section 1.3.

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the Cardiovascular, Respiratory, Gastrointestinal, Neurological, Musculoskeletal, and Hepatic systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.4.2 Vital signs

Pulse rate, respiratory rate, BP, and body temperature will be assessed as outlined in the Schedule of activities (see Section 1.3).

Body temperature may be measured by either oral or aural route at the discretion of the site, but must be performed using the same method in any individual study participant on all occasions.

Blood pressure measurements will be performed in both supine and standing positions for orthostatic measurement at Screening (supine BP after the study participant has been lying down for 5 minutes and then standing BP after 1 minute and 3 minutes) and in a supine position for routine BP measurements at all assessments. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by ≥5 minutes of rest for the study participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 BP measurement.

8.4.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

All ECG recordings should be taken with the study participant resting in the supine position for ≥5 minutes before the recording.

At each time point at which Triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 to 3 minutes apart. The full set of triplicates should be completed in less than 9 minutes.

8.4.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of activities (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those, which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the study participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study medication should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of activities (Section 1.3).

If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.4.5 Suicidal risk monitoring

All study participants will undergo suicidal risk evaluation at Screening and at the time points indicated on the Schedule of activities (Section 1.3).

Padsevonil is considered to be an AED. Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled studies of AEDs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for PSL.

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for Screening as well as to assess suicidal ideation and behavior that may occur during the study. All study participants will complete the "Screening" version of the C-SSRS at Screening (assessing the past 6 months) and the "Baseline" Version of the C-SSRS at Day -1, followed by Day 8, Day 13, and at SFU, as indicated on the Schedule of activities (Section 1.3).

Study participants being treated with PSL should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Families and caregivers of study participants being treated with PSL should be instructed to monitor study participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator. Consideration should be given to discontinuing PSL in study participants who experience signs of suicidal ideation or behavior.

8.4.6 Psychiatric and mental status

All study participants will undergo psychiatric/mental status evaluation at Screening and at the time points indicated on the Schedule of activities (Section 1.3).

The psychiatric and mental status of participating study participants will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms.

The parameters that will be evaluated are orientation, attention, memory, mood, calculus, behavior, and thinking or feeling. These parameters will be assessed as normal or abnormal and then determined whether clinically significant. If present and abnormal, psychiatric symptoms, mental impairment, and behavioral problems will be assessed as to whether they are clinically significant.

8.5 Adverse events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the study participant (or, when appropriate, by a caregiver, surrogate, or the study participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the study participant to discontinue PSL or UP0083 (see Section 7).

8.5.1 Time period and frequency for collecting adverse events and serious adverse events information

All AEs and SAEs will be collected from the signing of the ICF and at the time points specified in the Schedule of activities (Section 1.3).

Medical occurrences that begin before the start of study medication but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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 study medication), up to 30 days from the end of the study for each study participant, and to also inform 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 study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.5.2 Method of detecting adverse events and serious adverse events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the study participant is the preferred method to inquire about AE occurrences.

8.5.3 Follow up of adverse events and serious adverse events

After the initial AE/SAE report, the Investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 8.5.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow up (as defined in Section 7.3). Further information on follow up procedures is given in Appendix 3 (Section 10.3).

8.5.4 Regulatory reporting requirements for serious adverse events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of study participants and the safety of a study medication under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected SARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5 Pregnancy

Details of all pregnancies in female partners of male study participants will be collected after the start of study medication and until 30 days after the birth for any significant medical issues. In certain circumstances, the Sponsor 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. The Sponsor's Patient Safety (PS) department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

If a partner pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.5.6 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 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.

8.6 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 study medication so that investigators, clinical study participants, regulatory authorities, and IRB/IECs will be informed appropriately and as early as possible.

The UCB 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 study medication, 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.

8.7 Treatment of overdose

For this study, any dose of PSL greater than that prescribed in the protocol will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose. Padsevonil will not be self-administered by the study participant.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities until study medication can no longer be detected systemically (≥3 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study medication if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the study participant.

8.8 Genetics

Whole blood samples will be collected for CYP2C19 genotyping during the Screening Period, as specified in the Schedule of activities (Section 1.3). After CYP2C19 genotyping, the study participants will be grouped as described in Section 4.1.

Archive blood samples for exploratory genotyping of drug metabolizing enzymes, drug transporters, and other biomarkers will be collected as specified in the Schedule of activities (Section 1.3).

Instructions and additional details regarding CYP2C19 and exploratory genotyping sampling are provided in the Laboratory Manual.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP). Deviations in analyses from the final SAP will be documented in the clinical study report.

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set: All study participants who signed the informed consent.
- Safety Set (SS): All enrolled study participants who received at least 1 dose of PSL.
- Pharmacokinetic Per Protocol Set (PK-PPS): PK-PPS is a subset of the SS, consisting of those study participants who had no important protocol deviations affecting the PK parameters and for whom a sufficient number of samples are available to determine at least 1 PK parameter.

9.2 General statistical considerations

Statistical evaluation will be performed by the Sponsor or designee and supervised by the Early Development Statistics Department of UCB. All statistical analyses will be performed using SAS® Version 9.4 or later (SAS Institute, Cary, NC, USA).

For continuous variables, summary statistics will include number of study participants, mean, median, standard deviation, minimum, and maximum (geometric mean and geometric coefficient of variation [CV] for plasma concentrations and PK parameters). Categorical endpoints will be summarized using number of study participants, frequency, and percentages. Missing data will not be imputed. Individual plasma concentration and PK parameters will be presented using 3 significant digits.

If not otherwise stated, Baseline will be the last assessment prior to dosing. Measurement of specific Baseline values will be described in the SAP.

9.3 Planned efficacy/outcome analyses

9.3.1 Analysis of the primary efficacy/primary endpoint

As efficacy was not evaluated in this study, there will be no primary efficacy endpoint.

9.4 Planned pharmacokinetic analysis

Pharmacokinetic parameters of PSL and its metabolites ([redacted] and [redacted] in plasma (C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, CL/F, $C_{max,ss}$, $t_{max,ss}$, AUC_{τ}, and CL_{ss}/F) will be estimated using noncompartmental analysis with Pharsight Phoenix® WinNonlin® v6.3 (or higher) software. Other PK parameters of PSL and its metabolites in plasma or urine will be derived with SAS v9.4 (or higher). For calculation of the plasma PK parameters, the actual blood sampling time points will be used in order to determine the PK parameters. The calculation of metabolite to parent ratio (m/p), based on C_{max} and AUC will be described in the SAP.

All PK analyses will be performed using the PK-PPS. Distribution of the CYP2C19 genotypes will be presented. The individual plasma concentration of PSL and its metabolites will be summarized by genotype group and nominal sampling time, and PK parameters of PSL and its metabolites will be summarized by genotype group using descriptive statistics (number of observations (n), geometric mean, lower and upper 95% confidence interval (CI), geometric CV, arithmetic mean, standard deviation, CV, median, minimum, and maximum) and graphical displays.

The following PK parameters of PSL and its metabolites between genotype groups will be graphically displayed (scatter plot, box plot) and compared using analysis of variance on the log-transformed parameters and estimation of the geometric ratio of PK parameters between genotype groups with their 90% CI will be provided for:

- Single-dose: PSL and metabolites: C_{max}, $AUC_{(0-t)}$, AUC, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, A_e, f_e and CL_r; PSL metabolites: CL_{form}.
- Multiple-dose: PSL and metabolites: $C_{max,ss}$, AUC_{τ}, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, CL_{ss}/F, A_e, f_e, CL_r; PSL metabolites: CL_{form}.

The 3 comparisons of interest are the following (in sequential ordering):

- EM versus PM.
- Intermediate metabolizer (IM) versus PM.
- EM versus IM.

The comparison "EM versus PM" will be firstly evaluated and then the 2 other comparisons against IMs only if the comparison EM versus PM is nonequivalent.

Interpretation of results will be performed by comparing the 90% CI interval of geometric mean ratio with the acceptance range of 50% to 200%.

9.5 Planned safety analyses

All safety analyses will be performed using the SS. All safety variables will be listed and summarized by genotype group and time point.

Individual listings of AEs will be provided. These listings will include the following information: gender, age, body height, body weight, race, genotype group, system organ class (SOC), and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA®), AEs as reported, start and end with relative days to study medication administration, duration, intensity, seriousness and relationship to study medication, action taken, and final outcome. The start and stop of each AE will be given as absolute and relative to the time of study medication administration.

A treatment-emergent adverse event (TEAE) is defined as any event that emerges during treatment having been absent pretreatment, or worsens relative to the pretreatment state. Treatment-emergent AEs will be summarized in frequency tables displayed by SOC and PT according to MedDRA. The incidence of TEAEs and drug-related TEAEs will be summarized, ordered by primary SOC and PT.

The incidence of TEAEs will also be summarized in frequency tables by intensity.

Safety laboratory measurements, vital signs, and 12-lead ECGs parameters will be tabulated by group and period using descriptive statistics.

Data of assessment of suicidality (C-SSRS) will be listed.

Physical examinations abnormalities will be listed.

9.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol, which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant. Furthermore, study participants will be excluded from PK-PPS only when there is documented evidence that they received no treatment. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the relevant protocol deviation specification document, which is part of the study Data Cleaning Plan. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented

algorithmically to ensure consistency in the classification of important protocol deviations across all study participants.

9.7 Handling of dropouts or missing data

The methods for handling dropouts will be described in the SAP. Data of study participants prematurely terminating the study will be used to the maximum possible extent. No procedures for replacing missing data are intended. If a Baseline value is missing or not reliable, the last value before administration of study medication will serve as Baseline.

9.8 Planned interim analysis and data monitoring

No formal interim analyses are planned. Details about the safety analyses will be provided in the SMC Charter.

9.9 Determination of sample size

Considering the primary objective, and based on UP0057 (with PSL 100mg BID), the inter-participant CV of AUC_τ was estimated to be 39% (PSL). Using an inter-participant CV of 39%, a total sample size of 33 study participants (11 study participants per CYP2C19 genotype group) provides approximately 80% power for concluding that CYP2C19 genotype has no impact on the PK (using acceptance range of 0.5 to 2.0) based on expected ratio of 1.3 in PSL AUC_τ between CYP2C19 groups at a significance level of α=0.05.

In order to account for dropouts, the sample size will be increased by 20% (in total 39 study participants).

If more than 2 study participants dropout in each group, additional study participants will be recruited at the discretion of the Investigator and Sponsor.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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

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

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to 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 IRB/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 IRB/IEC as allowed.

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or contract research organization agreements, as applicable.

10.1.3 Informed consent process

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 legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The study participant or his 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 medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

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

The study participant may withdraw his consent to participate in the study at any time. A study participant is considered as enrolled in the study when he 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 written consent to participate in the study.

10.1.4 Data protection

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 IRB/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).

The study participant must be informed that his personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the study participant.

The study participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

The SMC will always be comprised of the Investigator, the Sponsor's medical representative, the scientific lead, and a PK expert where appropriate. Other experts may be included in this group or consulted at the discretion of the Sponsor.

10.1.6 Data quality assurance

All study participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of study participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

All essential documents are to be retained by the Investigator until ≥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 ≥2 years have elapsed since the formal discontinuation of clinical development of the study medication/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 relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

10.1.6.1 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 should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted.

Corrections made after the Investigator's review and signature of the completed eCRF will be resigned and dated 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.

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic 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 electronic eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.6.2 Apps

Not applicable.

10.1.7 Source documents

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).

10.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. The study site will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of study participants by the Investigator
- Discontinuation of further study medication development

10.1.9 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
Hematology[a]	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH % Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a,b]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (unfasted)	Calcium	ALP	
Routine Urinalysis[a]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Drug screen (to include at minimum: amphetamines, cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV-1/2 Ab, HBsAg, HCV-Ab, syphilis) The results of each test must be entered into the eCRF.			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-1/2=human immunodeficiency virus-1/2; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; RBC=red blood cells; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cells

[a] Hematology, clinical chemistry, and urinalysis asssessments will be performed under fasting conditions at Screening and Day -1, and nonfasting conditions at all other assessments.

[b] Details of liver chemistry stopping criteria and required actions and follow up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6. All events of ALT ≥3×upper limit of normal (ULN) and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse events – definitions and procedures for recording, evaluating, follow up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected DDI. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the study participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the study participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.1 Recording and follow up of adverse events and/or serious adverse events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the study participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the study participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the** Investigator **always make an assessment of causality for every event before the initial transmission of the SAE data to** UCB**.**
- The Investigator may change his opinion of causality in light of follow up information and send a SAE follow up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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.
- If a study participant dies during participation in the study or during a recognized follow up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the UCB within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB Study Physician by telephone.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE Reporting to UCB via Paper eCRF

- Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the UCB Study Physician.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Contraception guidance

10.4.1.1 Male study participants

Male study participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the Treatment Period and for ≥7 days after the last dose of study medication (Section 5.1):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10-1 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition male study participants must refrain from donating sperm for the duration of the study and for ≥7 days after the final dose of study medication.

Male study participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the Treatment Period and for ≥7 days after the last dose of study medication.

Table 10-1: Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [b]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of child bearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the study participant.

NOTES:
[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for study participants participating in clinical studies.
[b] For females, hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for ≥90 days after the last dose of study medication.

10.4.1.2 Collection of pregnancy information

Male study participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male study participant is in this study. This applies only to male study participants who receive study medication.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be ≥12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – suggested actions and follow up assessments

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

Investigators should attempt to obtain information on study participants in the case of study medication 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 study medication discontinuation and/or study participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB Study Physician and the Investigator for study participants who have ALT >5 ULN. The monitoring plan should include any necessary follow up assessments (until resolution of the abnormal lab values).

Phase 1 liver chemistry stopping criteria are designed to assure study participant safety and to evaluate liver event etiology (Table 10-2).

Table 10-2: Phase 1 liver chemistry stopping criteria and follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥3xULN If ALT ≥3xULN **AND** bilirubin ≥2xULN (>35% direct bilirubin) or INR >1.5, report as a SAE[a,b] See additional actions and follow up assessments below

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study intervention. • Report the event to UCB **within 24 hours.** • Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE[b]. • Perform liver function follow up assessments. • Monitor the study participant until liver function test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). • Consider the need for a toxicology screening. **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5** • Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow up assessments within **24 hours.** • Monitor study participant twice weekly until liver function test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. • **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow up assessments within **24 to 72 hours.** • Monitor study participants weekly until liver function abnormalities resolve, stabilize, or return to Baseline.	• Viral hepatitis serology[c]. • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥ 2xULN. • Complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF. **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in study participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic

	resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs.

Ab=antibody; AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransaminase; CPK=creatine phosphokinase; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to study participants receiving anticoagulants.

[c] Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

10.7 Appendix 7: Medical device incidents – definition and procedures for recording, evaluating, follow up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
BP	blood pressure
cBZR	central benzodiazepine receptor
CI	confidence interval
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
CPMP	Committee for Proprietary Medicinal Products
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic Case Report Form
EM	extensive metabolizer
FDA	Food and Drug Administration
GABAA	gamma-aminobutyric acid type a receptor alpha1 subunit
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intermediate metabolizer
IMP	investigational medicinal product
IRB	Institutional Review Board
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
PDILI	potential drug-induced liver injury

PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per Protocol Set
PM	poor metabolizer
PS	Patient Safety
PSL	padsevonil
PT	preferred term
QTc	QT interval corrected
QTcB	QT interval corrected for Bazett's formula
QTcF	QT interval corrected for Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	single dose
SFU	Safety Follow-up
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

10.11 Appendix 11: Protocol amendment history

Not applicable.

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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

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