AN OPEN-LABEL, PARALLEL-GROUP, PHARMACOKINETIC STUDY OF PADSEVONIL IN STUDY PARTICIPANTS WITH EITHER NORMAL HEPATIC FUNCTION OR WITH MODERATELY IMPAIRED HEPATIC FUNCTION (CHILD-PUGH CLASS B)

PROTOCOL UP0056

PHASE 1

Short title:

A pharmacokinetic, safety, and tolerability study of padsevonil in healthy study participants or those with moderate hepatic insufficiency

Sponsor:

UCB Biopharma SPRL

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Regulatory agency identifying number(s):

IND Number:	135622

Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Original Protocol	02 Jul 2019	Not applicable

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	USA: +1 800 880 6949 or +1 866 890 3175
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

An open-label, parallel-group, pharmacokinetic study of padsevonil in study participants with either normal hepatic function or with moderately impaired hepatic function (Child-Pugh Class B)

Short title:

A pharmacokinetic, safety, and tolerability study of padsevonil in healthy study participants or those with moderate hepatic insufficiency

Rationale:

Padsevonil (PSL) is currently being investigated for the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy. Epilepsy is a disorder that increases significantly with age (Kilpatrick and Lowe, 2002). Impairment of renal and hepatic function is common in the elderly and may alter metabolism and excretion of a drug and its metabolites. Thus, PSL is likely to be administered in patients who have impaired hepatic function and, as a consequence, this may impact the efficiency of the study drug.

This study aims to evaluate the effect of moderate hepatic insufficiency on pharmacokinetic (PK), safety, and tolerability following single and multiple oral doses of PSL. Padsevonil is predominately cleared hepatically, and hepatic insufficiency may affect some pathways of hepatic/gut drug metabolism and has also been associated with other changes, such as changes in absorption, plasma protein binding, transport, and tissue distribution. As PSL is predominantly hepatically cleared, impairment of hepatic function anticipates increased exposures. These changes may be particularly prominent in patients with impaired hepatic function (CPMP/EWP/2339/02, 2005; Food and Drug Administration [FDA] Guidance for Industry, 2003).

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the plasma PK of PSL in hepatically impaired and non-hepatically impaired study participants	• Single dose: C_{max}, AUC_{0-t}, AUC • Multiple dose: $C_{max,ss}$, AUC_{τ}
Secondary	
• To evaluate the safety and tolerability of PSL in hepatically impaired and non-hepatically impaired study participants	• Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation
Other	
• To evaluate plasma PK of PSL and its major metabolites ([redacted] and [redacted] in hepatically impaired and non-hepatically impaired study participants	<u>For PSL metabolites:</u> • Single dose: AUC, $AUC_{0-t,}$ and C_{max} • Multiple dose: AUC_{τ} and $C_{max,ss}$ <u>For PSL and its metabolites:</u> • Single dose: t_{max}, $t_{1/2}$, $AUC_{0-12,}$ and metabolic ratios of AUC and C_{max} • Multiple dose: t_{max}, $t_{1/2,\ ss}$, C_{trough}, metabolic ratios of AUC_{τ} and $C_{max,ss}$ <u>For PSL:</u> • Single dose: CL/F • Multiple dose: CL_{ss}/F • Bound and unbound plasma concentration of PSL in 2 samples.
• To evaluate the urine PK of PSL and its major metabolites ([redacted] and [redacted] in hepatically impaired and non-hepatically impaired study participants	• Amount excreted and metabolic ratio of amount excreted, CL_R, and f_e
• To evaluate the safety and tolerability of PSL in hepatically impaired and non-hepatically impaired study participants	• Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis) • Changes in vital signs (PR, BP, RR, and body temperature) • Changes in 12-lead ECG assessment • Physical examination findings

BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic(s); PSL=padsevonil; PR=pulse rate; RR=respiratory rate; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Overall design

This is a Phase 1, open-label study to evaluate the effect of moderate hepatic insufficiency on PK, safety, and tolerability following single and multiple oral doses of PSL.

The study includes a total of up to 24 study participants (Cohort A [approximately 12 participants] with normal hepatic function, and Cohort B [approximately 12 participants] with moderate hepatic insufficiency).

All cohorts will be initially matched for gender and then subsequently by weight to allow comparison across cohorts, if feasible. In each group there will be a homogenous repartition between male and female study participants with at least 2 study participants per gender.

Screening of study participants will be up to 28 days prior to entry into the clinic. Prior to the start of the open-label, Single-Dose Treatment Period, the participants will check in to the clinic and complete Baseline procedures and assessments preceding the first administration of study medication. This will then be followed by a Washout Period before the start of a Multiple-Dose Treatment Period. A second Washout Period will be undertaken before the participants have their End of Study (EOS) Visit. Please see the Schedule of Activities (Table 1-3) for more specific details.

Number of participants

Up to 24 study participants will be enrolled overall. Approximately 12 study participants per cohort will be included. Dropouts will be replaced at the discretion of the Investigator and Sponsor.

Treatment groups and duration

The maximum total duration for the study participants is 46 days; it will consist of a Screening Period, Baseline, 2 Treatment Periods, 2 Washout Periods, and an EOS Visit.

1.2 Schema

A table of criteria to define Child-Pugh score along with classification for hepatic insufficiency is presented in Table 1-1. For those participants with hepatic insufficiency, only study participants classified as moderate with a Child-Pugh score of 7 to 9 inclusive will be enrolled. A detailed schematic diagram of the study is provided in Table 1-2.

Table 1-1: Criteria to determine Child-Pugh score

Measure	1 Point	2 Points	3 Points
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (sec prolonged),	<4	4 to 6	>6
OR INR (ratio)	<1.70	1.70 to 2.30	>2.30
Ascites	Absent	Slight	Moderate or participant is on medication(s) to control ascites
Hepatic encephalopathy	None	Grade 1 or 2	Grade 3 or 4 or participant is on medication(s) to prevent encephalopathy

Total points	Hepatic insufficiency classification
5 to 6	A-Mild
7 to 9	B-Moderate
10 to 15	C-Severe

INR=international normalized ratio

Table 1-2: Study design

Cohort A (Healthy Study Participants) and Cohort B (Child-Pugh Hepatic Insufficiency Classification of Moderate) (n=approximately 12 per cohort)											
	Single Dose			Multiple Dose							
	Treatment Period	Washout Period		Treatment Period						Washout Period	EOS/ETV
Day	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12 (AM)**	**12 (PM)**	**13 to 17**	**18**
PSL Dose (mg)	100 AM only			100 BID	100 BID	100 BID	100 BID	100 AM only			
Blood Sample	PK	PK (each day)		PK	PK	PK	PK	PK	PK	PK (until Day 17)	
Urine Sample	PK	PK (each day)						PK			

BID=twice daily; EOS=End of Study; ETV=Early Termination Visit; PK=pharmacokinetic; PSL=padsevonil

1.3 Schedule of Activities

The Schedule of Activities is presented in Table 1-3.

Table 1-3: Schedule of activities

				Single Dose			Multiple Dose						
Procedures	**Screening**	**Baseline**		**Treatment Period**	**Washout Period**		**Treatment Period**					**Washout Period**	**EOS**[a] ETV
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12**	**13 to 17**	**18**
Written informed consent	X												
Admit to clinic		X[b]	X										
Demographics and baseline characteristics	X		X										
Inclusion/Exclusion criteria verification	X		X										
General medical/medications/ procedures history	X		X										
Participant identification card assigned			X										
Determination of the Child-Pugh class	X												
Suicidality Risk Assessment (C-SSRS)[c]	X		X								X		X
Physical examination[d]	X		X								X		X
Psychiatric and mental status evaluation	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs[e]	X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[f]	X		X										X

Table 1-3: Schedule of activities

				Single Dose			Multiple Dose						
Procedures	**Screening**	**Baseline**		**Treatment Period**	**Washout Period**		**Treatment Period**					**Washout Period**	**EOS**[a] ETV
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12**	**13 to 17**	**18**
Determination of the prothrombin and INR values	X												
Hematology, serum chemistry, urinalysis[g]	X		X				X				X		X
Serology (HIV, HepB and HepC)	X												
12-lead ECG[h]	X		X	X			X	X	X	X	X		X
Urine and cotinine drug screen, and alcohol breath test	X		X										
Recording of adverse events/medical procedures	X		X	X	X	X	X	X	X	X	X	X	X
Administer PSL				X			X	X	X	X	X		
Study drug accountability				X			X	X	X	X	X		
Blood sampling for PSL PK levels[i]				X	X		X	X	X	X	X	X	
Additional blood sample PPB[j]											X		
Urine collection for PSL PK[k]				X	X						X		

Table 1-3: Schedule of activities

				Single Dose			Multiple Dose						
Procedures	**Screening**	**Baseline**		**Treatment Period**	**Washout Period**		**Treatment Period**					**Washout Period**	**EOS[a] ETV**
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12**	**13 to 17**	**18**
Discharge from clinic													X

CBC=complete blood count; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=End of Study; ETV=Early Termination Visit; h=hour(s); Hep B=hepatitis B; Hep C=hepatitis C; HIV=human immunodeficiency virus; INR=international normalized ratio; PK=pharmacokinetic; PPB=plasma protein binding; PSL=padsevonil; WOCBP=women of childbearing potential

[a] If a participant discontinues early, EOS procedures should be completed as the ETV. Upon early termination/withdrawal, the study participant will be encouraged to complete the Washout Period and complete EOS assessments following the last dose of study medication.

[b] For convenience, the study participant may check-in to the clinic on the evening of Day -2. No study procedures will take place on Day -2. Study participants will be confined to the clinic from the time of check-in until check-out on Day 18.

[c] All study participants will complete the "Screening/Baseline" version of the C-SSRS during Screening (assessing the past 6 months) and Baseline (Day -1), followed by the "Since Last Visit" version at subsequent visits.

[d] Complete physical examinations will be performed on the days indicated. A brief physical examination will be conducted in a symptom-directed manner and only if clinically indicated (Section 8.4.1).

[e] Vital signs will be performed before each morning dose of PSL, and if feasible, at the same times as ECGs are performed.

[f] A serum pregnancy test will be performed for each WOCBP at Screening and a urine pregnancy test will be performed at any subsequent time points.

[g] Laboratory safety assessments (hematology, chemistry, and urinalysis) will be performed before the morning dose of PSL.

[h] A 12-lead ECG will be performed after a rest of at least 5 minutes. All ECG recordings will be performed in triplicate and should be sufficiently separated so they have a different 'minute' on the timestamp, and all are done within 4 minutes.

[i] Pharmacokinetic blood samples will be taken at the following time points: Predose and 15 minutes, 30 minutes, 45 minutes, 1h, 1.5h, 3h, 4h, 5h, 6h, 8h, 12h, 24h (Day 2), 48h (Day 3), 72h (Day 4), and 96h (Day 5) postdose. On Days 8, 9, 10, and 11, PK samples will be taken at predose. On Day 12, PK blood samples will be taken at the following time points: predose and 15 minutes, 30 minutes, 45 minutes, 1h, 1.5h, 3h, 4h, 5h, 6h, 8h, 12h, 24h (Day 13), 48h (Day 14), 72h (Day 15), and 96h (Day 16) postdose.

[j] Two blood samples will be collected after multiple doses at steady state (Day 12 predose and 1.5h postdose [~t_{max}]) for PPB.

[k] Urine for PK assessment will be collected from all study participants on Day 1 at predose and from 0h to <12h and 12h to <24h, on Day 2 from 24h to <48h, on Day 3 from 48h to <72h, on Day 4 from 72h to <96h, (before the 8am cutoff on Day 5) postdose. Urine for PK assessment will also be collected from all study participants on Day 12 from 0h to <12h postdose.

2 INTRODUCTION

2.1 Study rationale

Padsevonil is a novel chemical entity with selective affinity for both presynaptic vesicle protein 2 (SV2) isoforms and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid type A ($GABA_A$) receptor that has shown compelling, broad-range efficacy in several preclinical models of epilepsy conducted by UCB. Padsevonil is cleared via metabolism involving the cytochrome (CYP) pathway; the formation of the 2 major metabolites, [redacted] and [redacted]), is mainly mediated by CYP3A4, with potential involvement of CYP2C19. Padsevonil is currently being investigated for the treatment of focal onset seizures in adult patients with drug-resistant epilepsy. Epilepsy is a disorder that increases significantly with age (Kilpatrick and Lowe, 2002). Impairment of renal and hepatic function is common in the elderly and may alter metabolism and excretion of a drug and its metabolites. Thus, PSL is likely to be administered in patients also with hepatic insufficiency.

Hepatic impairment can adversely affect some pathways of hepatic and gut drug metabolism and has also been associated with changes in absorption, plasma protein binding, transport, and tissue distribution. As PSL is predominately cleared hepatically, changes in these absorption, distribution, metabolism, and excretion aspects may be expected in study participants with impaired hepatic function (CPMP/EWP/2339/02, 2005; FDA Guidance for Industry, 2003).

Therefore, UP0056 is designed to evaluate the effect of moderate hepatic insufficiency on the PK, safety, and tolerability of PSL given orally either as a single dose or multiple doses.

2.2 Background

More than 50 million people worldwide experience epilepsy (World Health Organization [WHO], 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 $GABA_A$ receptor mediates the bulk of inhibitory neurotransmissions in the brain. Allosteric modulation of inhibitory $GABA_A$ receptors by the 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 $GABA_A$ 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 the 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 $GABA_A$ 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 therapy in the treatment of focal-onset seizures in adult patients with drug-resistant 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 adverse effects 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” (Loganathan et al, 2015; Clemens, 2005). 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 effects in these 3 study participants administered PSL highlights the need to consider the possibility of significant psychiatric adverse effects and to maintain vigilance for such effects. The mitigation plan for acute psychiatric effects involves gradual titration and taper, which are known to improve tolerability of AEDs.

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 studies 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 initial clinical efficacy studies, and all echocardiograms were assessed as normal. There are currently no clinical data to suggest that the drug has an adverse effect 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 $GABA_A$-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use. As a precaution, and in view of the nonclinical histopathological cardiac findings, echocardiogram screening of study participants at Baseline and ongoing echocardiogram monitoring during treatment and post-treatment 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 study participants (healthy participants and those with moderate hepatic insufficiency) 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: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the plasma PK of PSL in hepatically impaired and non-hepatically impaired study participants	• Single dose: C_{max}, AUC_{0-t}, AUC • Multiple dose: $C_{max,ss}$, AUC_{τ}
Secondary	
• To evaluate the safety and tolerability of PSL in hepatically impaired and non-hepatically impaired study participants	• Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation
Other	
• To evaluate plasma PK of PSL and its major metabolites [redacted] and [redacted] in hepatically impaired and non-hepatically impaired study participants	For PSL metabolites: • Single dose: AUC, $AUC_{0-t,}$ and C_{max} • Multiple dose: AUC_{τ} and $C_{max,ss}$ For PSL and its metabolites: • Single dose: t_{max}, $t_{1/2}$, $AUC_{0-12,}$ and metabolic ratios of AUC and C_{max} • Multiple dose: t_{max}, $t_{1/2,\ ss}$, C_{trough}, metabolic ratios of AUC_{τ} and $C_{max,ss}$ For PSL: • Single dose: CL/F • Multiple dose: CL_{ss}/F • Bound and unbound plasma concentration of PSL in 2 samples.
• To evaluate the urine PK of PSL and its major metabolites ([redacted] and [redacted] in hepatically impaired and non-hepatically impaired study participants	• Amount excreted and metabolic ratio of amount excreted, CL_R, and f_e
• To evaluate the safety and tolerability of PSL in hepatically impaired and non-hepatically impaired study participants	• Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis) • Changes in vital signs (PR, BP, RR, and body temperature) • Changes in 12-lead ECG assessment • Physical examination findings

BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic(s); PSL=padsevonil; PR=pulse rate; RR=respiratory rate; SAE=serious adverse event; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

This is a Phase 1, open-label study to evaluate the effect of moderate hepatic insufficiency on PK, safety, and tolerability following single and multiple oral doses of PSL. The study design is shown in Table 1-2.

A study participant who provides written informed consent will be screened within 28 days of first Treatment Period. Baseline procedures will be performed within 1 day of the first Treatment Period. Study participants will be included in a single- and multiple-dose study of PSL. The study will include up to 24 study participants divided into 2 cohorts (Cohort A [approximately 12 participants] with no hepatic insufficiency and Cohort B [approximately 12 participants] with Child-Pugh classified moderate hepatic insufficiency).

Both cohorts will be initially matched for gender and then subsequently by weight to allow comparison across cohorts, if feasible. Hepatically impaired participants will be recruited first and subsequent sexes and weight matched controls will be included, if feasible. In each group there will be a homogenous repartition between male and female study participants with at least 2 study participants per gender.

All activities will be completed as per the Schedule of Activities (Table 1-3). Screening and Baseline assessments will be followed by the Single-Dose Treatment Period and a Washout Period before entering the Multiple-Dose Treatment Period. The participants will then then undergo a second Washout Period before completing the EOS Visit.

4.2 Scientific rationale for study design

In healthy volunteers without hepatic impairment, the concentration-time profiles of both PSL and [redacted] demonstrated a biphasic disposition with a terminal elimination half-life ($t_{1/2}$) of approximately 6 hours for the parent, and 10 to 14 hours for the metabolite, which were independent of dose. However, steady state was achieved after 2 to 3 days of treatment for both moieties, and the accumulation ratio for the parent was approximately 1.7 (range 1.59 to 2.11), which was greater than predicted by the single dose PK (N01386).

As PSL is cleared hepatically, exposure to drug in hepatically impaired participants could increase primarily due to a reduction in PSL clearance, among other factors. This can be illustrated by an increase in $t_{1/2}$, a prolonged washout time, and an increased time to reach steady state with multiple dosing. To facilitate the design of this study, a doubling of $t_{1/2}$ and time to steady state has been assumed in hepatically impaired participants. Therefore, the Washout Period required to capture the $t_{1/2}$ of the [redacted] has been calculated to be 5 to 6 days (assumes a $t_{1/2}$ of 28 hours) and the time to steady state has been calculated to be 4 to 6 days.

4.3 Justification for dose

The maximum tolerated dose (MTD) of PSL was identified as repeat dosing of 400mg twice daily (BID) in Phase 1 studies. In this study, the planned doses are well under the MTD, and

100mg BID is one of the dose levels currently being investigated in the 2 pivotal efficacy studies (EP0091 and EP0092). Padsevonil is predominantly cleared hepatically; therefore, an increase of exposure of PSL is expected in these hepatically impaired participants. A dose of 100mg BID was selected to allow collection of PK and tolerability data in vulnerable participants who may have less tolerance to PSL as compared with healthy participants. In addition, selection of a dose level of 100mg BID, which is 4-fold lower than the MTD, provides an opportunity to characterize the effect of liver disease on PSL PK without exploring PSL exposure beyond the one achieved at the MTD.

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the EOS Visit in the Schedule of Activities (Table 1-3).

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the study globally.

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

Participants are eligible to be included in the study only if all of the following criteria apply at Screening and at Baseline (Day -1):

Inclusion criteria for ALL study participants

1. Participant must be male or female 18 to 70 years of age, inclusive, at the time of signing the informed consent.
2. Participant must have body weight of at least 50kg (males) or 45kg (females) and body mass index within the range 18 to 38kg/m^2 (inclusive).
3. Participant must be 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) and in this protocol.
4. Participant must be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator, and must be capable of communicating satisfactorily with the Investigator.
5. Participants must meet the following requirements to be included in the study:
   - A male participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during both Treatment Periods and for at least 7 days after the last dose of study medication and refrain from donating sperm during this period.
   - A female participant is eligible to participate if she is not pregnant (see Appendix 4; Section 10.4), not breastfeeding, and at least 1 of the following conditions applies:

     Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)

OR
A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during both Treatment Periods and for at least 90 days (or 5 terminal half-lives) after the final dose of study medication.

Specific inclusion criteria for study participants WITHOUT hepatic insufficiency

6. Participants must be healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, and cardiac monitoring.

   Note: Participant has clinical laboratory test results within the local reference ranges or values that are considered not clinically relevant by the Investigator and approved by the UCB Study Physician. Laboratory parameters outside the reference ranges can be retested, and if the retest result is within the reference range or considered clinically not relevant, the study participant will be allowed in the study.

Specific inclusion criteria for study participants WITH moderate hepatic insufficiency

7. Participant must have characteristics that will meet the clinical criteria usually found in participants with chronic hepatic insufficiency, as determined by medical history and physical examinations (eg, echography, scintigraphy, biopsy, or some specific laboratory values as evidence) conducted within 3 weeks prior to the start of the Single-Dose Treatment Period. The degree of severity of hepatic impairment will be determined according to the classification of Child-Pugh (a score from 7 to 9 for Class B-moderate classification).

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply at Screening or at Baseline (Day -1):

Exclusion criteria for ALL study participants

1. Participant is, in the judgment of the Investigator, likely to be unreliable or noncompliant or uncooperative during the study.
2. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or 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 Screening Visit.
3. Participant has a known hypersensitivity to any components of the study medication as stated in this protocol. Participant has sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or UCB Study Physician, contraindicates participation in the study.
4. Participant has a lifetime history of suicide attempt (including an [redacted]), or [redacted] 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 or at Baseline (Day -1).

5. Participant has participated in another study of an investigational medicinal product (IMP) within the previous 1 month (or 5 half-lives, whichever is longer) prior to Screening, or is currently participating in another study of an IMP.
6. Participant has had 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.
7. Participant is unable to tolerate oral medication or has a history of gastrointestinal bypass surgery.
8. Participant has past or intended use of over-the-counter or prescription medication including herbal remedies and hepatic enzyme inhibitors within 2 weeks or 5 half-lives prior to dosing, particularly for participants with hepatic impairment where $t_{1/2}$ may be prolonged. Specific medications listed in Section 6.5.1 may be allowed. Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, phenytoin, isoniazid, or rifampicin, etc.) within 2 months prior to dosing unless required to treat an AE. This does not include oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy (HRT) or implants, patches, or intrauterine devices (IUDs) /intrauterine systems (IUSs) delivering progesterone (for female study participants) or acetaminophen with a maximal dose of 2g/day or with a maximum of 10g over 15 days. In case of uncertainty, the UCB Study Physician should be consulted.
9. Participant has a history of chronic alcohol or drug abuse within the previous 12 months. Participant has a positive pre-study drug/alcohol screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines). A participant with a positive finding on the drug screen may still be enrolled at the discretion of the Investigator if a plausible clinical explanation exists (eg, prior or concomitant medication use).
10. Participant has any clinically relevant ECG finding at the Screening Visit or at Baseline (Day -1). Participant has an abnormality in the 12-lead ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett's formula (QTcB) or Fridericia's formula (QTcF) >450ms in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval ≥220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out-of-range result, 1 repeat will be allowed. If the result is out-of-range again, the study participant cannot be included.

    NOTE A: The QTcB or QTcF is either machine-read or manually over-read.
    NOTE B: The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QT interval corrected (QTc) for an individual participant and then the lowest QTc value used to include or discontinue the participant.
11. Participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.

12. Participant has renal impairment as indicated by an estimated glomerular filtration rate (GFR) <60mL/min, calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, 2009):

    $GFR_{CKD\text{-}EPI} = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if Black]

    Where Scr is serum creatinine in mg/dL,

    κ is 0.7 for females and 0.9 for males,

    α is -0.329 for females and -0.411 for males,

    min indicates the minimum of Scr/κ or 1,

    and max indicates the maximum of Scr/κ or 1

13. Participant tests positive for human immunodeficiency virus-1/2 antibody (HIV-1/2Ab) at Screening or within 3 months prior to the first dose of study medication.
14. 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.
15. Participant has received blood or plasma derivatives within the 6 months preceding Screening.
16. 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).
17. Participant smokes more than 10 cigarettes per day (or equivalent) or has done so within 6 months prior to the Screening Visit.
18. Participant ingests grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) within 72h before each administration of study medication. If this is the case at the start of the study, study participants may be rescreened.
19. Female participant tests positive for pregnancy, plans to get pregnant during participation in the study, or is breastfeeding.
20. Participant has a diet that deviates notably from the "normal" amounts of protein, carbohydrate, and fat, as judged by the Investigator.
21. Participant has undergone sudden and/or extreme changes in exercise levels for 2 weeks prior to Screening Visit.

Specific exclusion criteria for study participants WITHOUT hepatic insufficiency

22. Participant has a history or presence of cardiovascular (eg, cardiac insufficiency, coronary heart disease, hypertension, arrhythmia, tachyarrhythmia, or myocardial infarction), 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. Symptomatic or asymptomatic orthostatic hypotension at Screening

defined as a 20mmHg or more decrease in SBP, or 10mmHg or more decrease in DBP after 1 and 3 minutes standing with the arm relaxed at the side (time zero begins after the study participant is upright). Five minutes of supine rest is used as baseline.

23. Participant tests positive for hepatitis B surface antigen, or Hepatitis C virus antibody (HCV-Ab) at Screening or within 3 months prior to the first dose of study medication.

    NOTE: Participants with positive HCV-Ab due to prior resolved disease can be enrolled if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test is obtained. The HCV RNA testing is optional and participants with negative HCV-Ab test are not required to also undergo Hepatitis C RNA testing.

24. Participant must have BP and pulse rate (PR) within normal range in the supine position after 5 minutes rest (SBP: 90mmHg to 150mmHg; DBP: 40mmHg to 95mmHg; PR: 40bpm to 100bpm). 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.

25. Participant has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0x upper limit of normal (ULN).

26. Participant has bilirubin >1.0xULN (isolated bilirubin >1.0xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

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

    If participant has >ULN ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the study participant must be discussed with the UCB Study Physician.

28. Participant has tests results with ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

29. Participant has gastrointestinal disease with the potential to influence absorption, including motility disorders.

Specific exclusion criteria for study participants WITH moderate hepatic insufficiency

Participants with moderate hepatic insufficiency will not be eligible for inclusion in this study if any of the following criteria apply at Screening or Baseline (Day -1):

30. Participant must have vital sign parameters defined as: supine BP after at least 5 minutes rest and standing after 1 and 3 minutes rest must be within normal range (SBP: 90mmHg to 180mmHg; DBP: 40mmHg to 105mmHg; PR: 50bpm to 100bpm).

31. Results of laboratory tests must be within the reference ranges except those usually found to be abnormal in study participants with moderate hepatic insufficiency. A study participant

with other values outside the normal range may be included in the study if, in the opinion of the Investigator, these values are of no clinical significance for the participant with moderate hepatic insufficiency and after approval of the UCB Study Physician has been obtained.

32. Participants with moderate hepatic insufficiency and derived and associated clinical and laboratory findings of moderate hepatic insufficiency are allowed as long as they do not have other clinically important systemic disease such as psychiatric illness, or uncontrolled diabetes (based on medical history, physical examination, ECG, and/or routine laboratory data). The study participant may not have diseases that might confound the results of the study or cause additional risks during administration of PSL.
33. Participant has acute liver failure of any etiology.
34. Participant has biliary cirrhosis.
35. Participant has used any drug indicated for the medical care of moderate hepatic insufficiency that is not established in dose and schedule for at least 14 days before the first liver function test (except paracetamol with a maximal dose of 2g/day or with a maximum of 10g over 15 days).

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Participants will complete a light meal 30 minutes prior to each morning dose of PSL and will complete a standard meal 30 minutes prior to the evening dose. The standardized meal composition and timing should be consistent for all days the participant is on study. 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.
- Padsevonil will be administered orally with 8oz (240mL) water. Between 1h predose and 2h postdose, the total intake of beverages should be limited to 100mL.
- The participant must not ingest grapefruit, starfruit, and pawpaw (as beverage, fruit, or supplements) within 72h before the study medication administration. These fruits are not allowed during the Treatment Period and throughout the study.

5.3.2 Caffeine, alcohol, and tobacco

- During dosing, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 48h before the start of dosing until after collection of the final PK sample.
- During the study, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.

5.3.3 Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests and during the study. Participants may participate in light recreational activities during the study (eg, watching television, reading).

5.4 Screen failures

Screen failures are defined as 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 participants to meet the Consolidated Standards of Reporting Trials 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. Study participants may be rescreened under conditions such as the following:

- Study participant ingests grapefruit (as beverage, fruit, or supplements) within 72 hours before each administration of study medication.
- If a study participant does not meet the enrollment criteria at Screening or on Day -1 due to an out-of-range laboratory result or a minor illness, he/she can be rescreened once at the discretion of the Investigator. Provided all enrollment criteria are met at the second screening, the study participant can be included.

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.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening and only applies to healthy participants.

Rescreened participants will be assigned a new participant number.

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

A summary of the treatments administered is provided in Table 6-1. Treatments will be administered in an open-label fashion and participants will be dosed in an upright position and will remain semi-recumbent until 4 hours after dosing.

Table 6-1: Study medications administered

Study Medication Name:	**Padsevonil**
Dosage formulation:	Tablets
Unit dose strength(s):	100mg
Route of administration:	Oral
Dosing instructions:	Dosing instructions are provided in the UP0056 IMP Handling Manual (IMP Instructions for Handling).
Packaging and labeling:	PSL tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws and regulations.
Manufacturer:	UCB

IMP=investigational medicinal product; PSL=padsevonil

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 medications received and any discrepancies are reported and resolved before use of the study medication.

Only participants enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medication 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 UP0056 IMP Handling Manual (IMP Instructions for Handling).

Further guidance and information for the final disposition of unused study medication are provided in the UP0056 IMP Handling Manual (IMP Instructions 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 procedures 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: randomization and blinding

This study is an open-label, non-randomized study; therefore, no study personnel or study participants will be blinded and no randomization will occur.

Each participant will receive a 5-digit number assigned at Screening that serves as the participant identifier throughout the study. The participant number will be required in all communication between the Investigator and designee.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study medication blind

This is not applicable as this is an open-label study.

6.3.1.2 Breaking the treatment blind in an emergency situation

This is not applicable as this is an open-label study.

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 use of concomitant medications during this study by participants without hepatic insufficiency should be avoided unless necessary to treat AEs or unless approved on a case-by-case basis prior to enrollment (eg, hormonal contraceptives). The use of any concomitant medications should be approved by the Sponsor in advance, in writing, when possible. The following concomitant medications are permitted during the study:

- Paracetamol for the treatment of mild symptoms (eg, headache or other pain), given at most every 6h to 8h, not exceeding 2g/day, and with a total of no more than 10g over 15 days.
- Inhaled corticosteroids for seasonal rhinitis.
- Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal HRT or implants, patches, or IUDs/IUSs delivering progesterone (for female participants).

Use of other chronic medication by study participants with moderate hepatic insufficiency, not interfering with the endpoints of the study and at the discretion of the UCB Study Physician, will be permitted.

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 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 UCB Study Physician 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 UCB 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.

6.7 Treatment after the end of the study

There are no plans for participant continued care 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 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. Investigators should contact the UCB Study Physician, in advance, whenever possible, to discuss the withdrawal of a participant. No restart will be allowed.

7.1.1 Liver chemistry stopping criteria

The liver stopping criteria in this study will differ between those participants with normal hepatic function and those with impaired hepatic function.

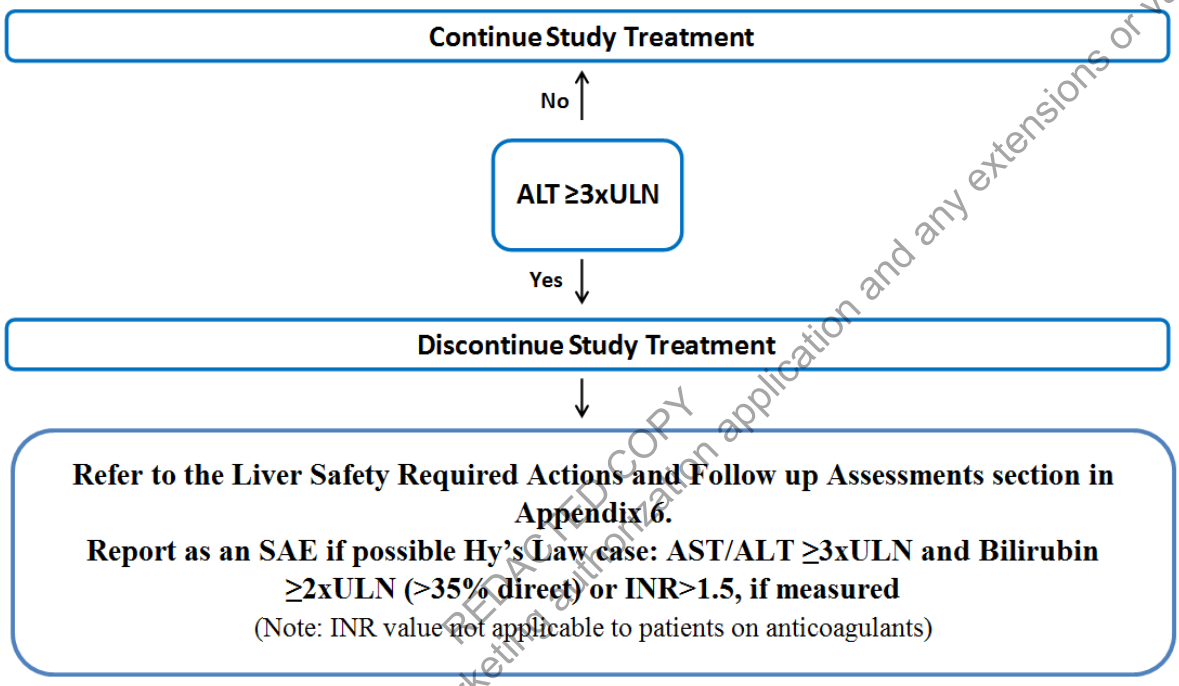
7.1.1.1 Participants with normal hepatic function

Discontinuation of study medication for abnormal liver function should be considered by the Investigator when a healthy participant meets 1 of the conditions outlined in Figure 7-1 or if the

Investigator believes that it is in best interest of the participant. Study medication will be discontinued immediately and permanently for a healthy participant if liver chemistry stopping criteria are met.

If clinically concerning deteriorations in liver chemistry findings occur in a participant with established moderate hepatic insufficiency, then study medication will be discontinued immediately and permanently.

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).

7.1.1.2 Participants with impaired hepatic function

In view of the differing degrees of hepatic impairments anticipated among this subset of participants, the fixed criteria detailed in Figure 7-1 are inappropriate.

Accordingly, any significant elevation of AST, ALT, bilirubin, or international normalized ratio (INR) values should be discussed with the UCB Study Physician and, in the context of the Baseline and pre-study levels typical for the individual and their overall clinical condition, a decision reached as to whether the case should be handled as a PDILI.

As a guide, a doubling of any value is expected to represent a threshold for this evaluation.

If a PDILI case is so identified, then the participant will be evaluated in accordance with the requirements of Appendix 6 (Section 10.6), adapted as necessary to match the circumstances.

7.1.2 Criteria for study hold 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 ARs
  - occur in the same body system, and
  - lead to the 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 Study Physician, Safety Physician, Clinical Project Manager, 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 (see Section 10.3).

7.2 Participant discontinuation/withdrawal from the study

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

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

If the 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 participant withdraws from the study, he/she 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 (Table 1-3) for data to be collected at the time of early termination/study discontinuation and follow up and for any further evaluations to be completed.

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 makes it unsafe to continue.
2. Participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Participant takes prohibited concomitant medications as defined in this protocol.
4. Participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requests withdrawal of the participant.
7. The study participant has changes in the ECG that are regarded as clinically significant and/or that worsen over time.
8. The study participant has an ECG that shows an absolute value for QTcB or QTcF ≥500ms or ≥60ms above Baseline.
9. The study participant develops a second- or third-degree atrioventricular block or another clinically relevant change in ECG as determined by the Investigator.
10. 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 the benefit/risk of continuing the study participant in the study on PSL.
11. 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.
12. 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 ≥0.5G/L.
  - Neutrophils absolute <1.5G/L.
  - Platelets absolute ≤100G/L.

Investigators should attempt to obtain follow-up information on study participants in the case of withdrawal.

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

Participants who are withdrawn will be replaced at the discretion of the Investigator and Sponsor.

7.3 Lost to follow up

A participant will be considered lost to follow up if he or she 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the 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 considering the participant lost to follow up, must be recorded in the source documents. The electronic eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she 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 (Table 1-3). Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 1-3), is essential and required for study conduct.

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

Procedures conducted as part of the 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.

The maximum amount of blood collected from each 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 Pharmacokinetics

Whole blood and urine samples will be collected for measurement of plasma and urine concentrations of PSL and its metabolites, as specified in the Schedule of Activities (Table 1-3).

Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24h clock time) of each sample will be recorded.

Samples collected for analyses of PSL plasma and urine concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

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. The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

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

The maximum deviations from scheduled sampling times considered irrelevant for PK are defined in Table 8–1.

Table 8–1: Irrelevant time deviations for PK sampling

PK blood sampling times	Deviation from scheduled time considered irrelevant
0 hours (predose)	Within 60 minutes predose
0.25 to 1.5 hours	2 minutes
2 to 8 hours	5 minutes
12 hours	15 minutes
24 to 96 hours	60 minutes

PK=pharmacokinetic

8.2 Plasma protein binding

Selected plasma samples (see Schedule of Activities, Table 1-3) will be collected and archived for future determination of ex-vivo plasma protein binding of PSL and, if feasible, its metabolites [redacted] and [redacted]. If these investigations are performed, they will be described and reported as an addendum to the clinical study report (CSR).

8.3 Pharmacodynamics

Not applicable.

8.4 Safety assessments

The safety and tolerability of a single or multiple doses of PSL will be monitored by evaluation of AEs, vital signs (oral body temperature, PR, respiratory rate [RR], BP), 12-lead ECG parameters, physical examination findings, suicidal risk monitoring, psychiatric and mental status examination, and clinical laboratory test results. Planned time points for all safety assessments are provided in the Schedule of Activities (Table 1-3).

8.4.1 Physical examination

Physical examinations will be performed at the time points specified in Table 1-3. A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; abdomen; assessments of the Cardiovascular, Respiratory, Gastrointestinal Neurological, Musculoskeletal, and Hepatic systems; and mental status. Height and weight will also be measured and recorded.

A brief physical examination will be conducted in a symptom-directed manor and only if clinically indicated. A brief physical examination will include, at a minimum, assessments of general appearance, 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

Oral temperature, PR, RR, and BP will be assessed.

Blood pressure and pulse measurements will be assessed in a supine position 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 at least 5 minutes of rest for the 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 ECGs will be obtained as outlined in the Schedule of Activities (see Table 1-3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.2 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.

8.4.4 Clinical safety laboratory assessments

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

The Investigator must review the laboratory reports, document this reviews, 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 laboratory findings that change considerably or that increased in frequency or intensity more than expected as compared with the clinical profile known to the Investigator from the study participant's history or Screening Period.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or at the EOS Visit should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or UCB Study Physician.

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 UCB Study Physician notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual or equivalent document and the Schedule of Activities.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in 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

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 (Columbia University Medical Center, 2008). 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/Baseline" version of the C-SSRS during Screening (assessing the past 6 months) and Baseline (Day -1), followed by the "Since Last Visit" version at the visits indicated on the Schedule of Activities (Table 1-3).

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 participants who have been treated with PSL should be instructed to monitor 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 Investigator. Consideration should be given to discontinuing PSL in participants who experience signs of suicidal ideation or behavior.

8.4.6 Psychiatric and mental status

The psychiatric and mental status of 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 Psychiatric and Mental Status assessment will be performed according to the Schedule of Activities (see Table 1-3). 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 participant.

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 participant to discontinue PSL or UP0056 (see Section 7).

8.5.1 Time period and frequency for collecting AE and SAE 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 (Table 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, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24h, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24h 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 participant, and to also inform 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 AEs and SAEs

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

8.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious 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 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 SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of 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, IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review the document and 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 participants and, if indicated, female partners of male participants will be collected after the start of study medication and until 12 months after the birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 12 months. If the study participant is lost to follow up and/or refuses to give information, written documentation of attempts to contact the study participant, or their female partner, needs to be provided by the Investigator and filed at the site. UCB'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 pregnancy is reported, the Investigator must immediately inform the Sponsor within 24h of learning of the pregnancy and should follow the procedures outlined in Appendix 4 Section 10.4).

The participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The participant should return for an Early Discontinuation Visit.
- The participant should immediately stop the intake of the study medication as instructed at the Early Discontinuation Visit.

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 be concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the 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, study participants, regulatory authorities, and IRBs/IECs can be informed appropriately.

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 Efficacy assessments

Not applicable.

8.8 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/or 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 UCB Study Physician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study medication can no longer be detected systemically (at least 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 UCB Study Physician (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 UCB Study Physician based on the clinical evaluation of the participant.

8.9 Genetics

Not applicable.

8.10 Biomarkers

Not applicable.

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 CSR.

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set: All study participants who have signed the informed consent.
- Full analysis Set (FAS): All enrolled study participants who received at least one dose of study medication. Analysis of this set will be according to the treatment the participants actually received.
- Pharmacokinetic Per Protocol Set (PK-PPS): the PK-PPS is a subset of the FAS, 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 one 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 three 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 safety and other analyses

9.3.1 Pharmacokinetic analyses

Pharmacokinetic parameters will be determined by non-compartmental analysis with Pharsight Phoenix® WinNonlin® v6.3 (or higher) software using the PK-PPS.

Pharmacokinetic parameters of PSL and its major metabolites ([redacted] will be computed using the actual blood sampling time points.

The plasma concentration-time profiles, urine amounts, and PK parameters of PSL and its metabolites will be summarized by cohort (group), treatment period, and day using descriptive statistics (number of available observations, arithmetic mean, standard deviation, geometric mean, and CV of the geometric mean, median, minimum, and maximum).

Individual plasma PSL and metabolites concentration-time profiles will be displayed graphically on a linear-linear scale and semi-logarithmic scale (including spaghetti plots). Geometric mean plasma concentrations-time curves, including 95% confidence intervals (CIs), will be displayed by cohort.

For the Single- and Multiple-Dose Treatment Periods, PK parameters (including AUC, AUC_{τ}, $C_{max,ss}$, and C_{max}) of PSL will be compared between the 2 cohorts (healthy and hepatically impaired participants) using analysis of variance (ANOVA) as follows: point estimates for the ratio of geometric means between healthy and hepatically impaired participants and the respective 2-sided 90% CIs will be computed using the least squares means and the root mean squares of error from the ANOVA of the log-transformed data with subsequent exponential transformation. Interstudy participant variability of PK parameters will be derived from these analyses.

Graphical representation of the data (eg, Scatter plots) and/or linear regression analysis of the primary PK parameters (AUC and C_{max}) of PSL and metabolites against the Child-Pugh parameters of total bilirubin, albumin, and prothrombin time will be also provided, if feasible.

9.3.2 Safety analyses

All safety analyses will be performed using the FAS. All safety variables will be listed and summarized by cohort.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment and treatment-emergent according to the intake of the study medication. The occurrence and incidence of treatment-emergent AEs (TEAEs) will be summarized by MedDRA system organ class and preferred term and by Treatment Period, intensity, and by cohort. The occurrence and incidence of TEAEs will also be summarized by intensity and relationship to the study medication as judged by the Investigator. Treatment-emergent adverse events leading to discontinuation and SAEs will also be summarized.

Laboratory variables and changes from Baseline will be summarized at each time point by cohort. Shift tables from Baseline to each post-Baseline time point will be presented. Values outside the reference range will be flagged in the listings. The out-of-normal range values will be displayed. Any PDILI events will be listed.

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

Electrocardiograms will be recorded 3 times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The individual mean and change from Baseline (time-matched Baseline day of each Treatment Period, when applicable) will be summarized by descriptive statistics at each time point by cohort.

Assessment of suicidality (C-SSRS) will be listed.

Physical examination abnormalities will be listed.

9.4 Planned efficacy/outcome analyses

As efficacy is not being evaluated in this study, there is no primary efficacy endpoint.

9.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol that potentially could have a meaningful impact on study conduct or on the primary PK outcomes for an individual study participant. Furthermore, study participants will be excluded from the FAS 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.

Important protocol deviations will be reviewed as part of an ongoing data cleaning process prior to database lock to confirm exclusion from analysis sets.

9.6 Handling of dropouts or missing data

The methods for handling dropouts will be described in the SAP.

Dropouts will be replaced at the discretion of the Investigator and Sponsor. 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.

9.7 Planned interim analysis and data monitoring

No interim analysis or data monitoring are planned in this study.

9.8 Determination of sample size

No formal sample size calculation is required for a hepatic insufficiency study. Up to 24 study participants will be included with approximately 12 participants per cohort; this is considered sufficient to meet the study objectives.

Based on the FDA guidance (FDA Guidance for Industry, 2003) regarding a two-fold change in AUC, exploratory sample size estimation was performed assuming the following:

- Log-normal distribution on AUC_{ss}
- Inter-study participant CV% of 40%
- Detection of a two-fold change in AUC_{ss}, which is equivalent to a 50% reduction in total body clearance

A sample size of 12 in each group will have >90% power to detect a fold change in means (expected ratio) of 2.000 assuming that the CV is 0.400 using a 2-sample t-test with a 0.050 1-sided significance level.

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-Good Clinical Practice (ICH-GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other 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 participants or others, and any protocol deviations, to eliminate immediate hazards to 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 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 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 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 clinical research organization agreements, as applicable.

10.1.3 Informed consent process

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

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

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

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

10.1.4 Data protection

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

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

The participant must be informed that his/her 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 participant.

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

10.1.5 Committees structure

Not applicable.

10.1.6 Data quality assurance

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

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 clinic records, charts, laboratory results, printouts, pharmacy records, ECG or other printouts, or completed scales, 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 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. Study sites 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 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 participants are detailed in Section 5.1 and Section 5.2 of this 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	Platelet Count	RBC Indices: MCV MCH Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
	Coagulation panel			
	INR			
Clinical Chemistry[a]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis[b]	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick. If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.			
Other Screening Tests	• Follicle-stimulating hormone (at Screening only) to confirm postmenopausal status in female study participants • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Pregnancy test: Serum human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential) • Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab) > The results of each test must be entered into the eCRF.			

[a] 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×ULN) and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT≥3×ULN and 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 insufficiency or cirrhosis).

[b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

10.3.1 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 drug-drug interaction.
- 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 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.

10.3.2 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).

An 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 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 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 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.

10.3.3 Recording and follow up of AE and/or SAE

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 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 participant identifiers, with the exception of the 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 one of the following categories:

- Mild: An event that is easily tolerated by the 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 one 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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she 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/her 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 participant is lost to follow up. This follow up requirement applies to AEs, SAEs, and AEs of special interest. • If a 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 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 CRF
• Facsimile transmission of the SAE paper CRF 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 CRF 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 Definitions

10.4.1.1 Woman of childbearing potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception guidance

10.4.2.1 Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in 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 WOCBP who is not currently pregnant.

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

Male 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 protocol-defined time frame and for 7 days after the final dose of study medication.

10.4.2.2 Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Serum beta human chorionic gonadotropin (hCG) pregnancy testing will be performed at Screening.
- Additional urine beta hCG pregnancy testing will be performed at predose on Day -1 and at the EOS/Early Termination Visit. The result must be negative prior to dosing the study participant.

10.4.2.3 Collection of pregnancy information

10.4.2.3.1 Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-1.

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 (IUD) • Intrauterine hormone-releasing system (IUS) • 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 WOCBP 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 participant.

[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 participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, an appropriate additional barrier method of contraception should be utilized during the Treatment Period and for at least 90 days after the final dose of study medication.

10.4.2.3.2 Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- 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 at least 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.

10.4.2.3.3 Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.5.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Genetics

Not applicable.

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

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 be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete a 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 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 >5x ULN and participants with hepatic impairment who show a doubling of their Baseline AST, ALT, bilirubin, or INR values. 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 participant safety and to evaluate liver event etiology (Table 10-2).

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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
For participants without hepatic insufficiency	
ALT-absolute	ALT≥3xULN If ALT ≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin) OR INR >1.5, report as an SAE.[a,b] See additional actions and follow up assessments listed below

Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• Report the event to the UCB **within 24 hours.** • Complete the liver event eCRF, and complete a SAE data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**. • Monitor participant twice weekly until liver chemistry 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 chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow up assessments within **24 to 72 hours**. • Monitor participants weekly until liver chemistry 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 creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN. • Obtain 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 high performance liquid chromatography

	(HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al, 2009].) **NOTE: Not required in China.** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs.
For participants with moderate hepatic insufficiency	
• Participants with moderate hepatic insufficiency whose liver function deteriorates dramatically on study medication will be managed in a comparable manner, in accordance with their hepatic status.	

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

a Serum bilirubin fractionation should be performed if testing is available. 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 insufficiency or cirrhosis). The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

c Hepatitis A IgM antibody; HBsAg and HCV-Ab; 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
ANOVA	analysis of variance
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
cBZR	central benzodiazepine receptor
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
$GABA_A$	gamma-aminobutyric acid type A
GCP	Good Clinical Practice
GFR	glomerular filtration rate
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCV-Ab	hepatitis C virus antibody
HIV-1/2Ab	human immunodeficiency virus-1/2 antibody
HRT	hormone replacement therapy
IB	Investigator's brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PR	pulse rate
PS	Patient Safety
PSL	Padsevonil
QTc	QT interval corrected
QTcB	QT interval corrected for Bazett's formula
QTcF	QT interval corrected for Fridericia's formula
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SBP	systolic blood pressure
SV2	synaptic vesicle protein 2
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

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

Name: UP0056-protocol

Version: 1.0

Document Number: CLIN-000134923

Title: UP0056-protocol

Approved Date: 09 Jul 2019

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 04-Jul-2019 06:34:15 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-Jul-2019 15:41:21 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 05-Jul-2019 19:15:52 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 09-Jul-2019 07:36:48 GMT+0000