AN OPEN-LABEL, PARALLEL-GROUP, PHARMACOKINETIC, SAFETY AND TOLERABILITY STUDY OF SINGLE AND MULTIPLE ORAL ADMINISTRATIONS OF PADSEVONIL IN ADULT AND ELDERLY STUDY PARTICIPANTS

PROTOCOL UP0053 AMENDMENT 1

PHASE 1

Short title:

An open-label pharmacokinetic and safety study of single and multiple administrations of padsevonil in adult and elderly study participants

Sponsor:
UCB Biopharma SPRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Regulatory agency identifying number(s):

IND Number:	135622

Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 1	29 May 2019	Nonsubstantial
Original Protocol	07 May 2019	Not applicable

Amendment 1 (29 May 2019)

Overall Rationale for the Amendment

The protocol has been amended to provide clarification regarding the collection of samples for safety laboratory evaluations, pharmacokinetics, and plasma protein binding. The timing was corrected for the collection of the samples for plasma protein binding and urine pharmacokinetics. The timing for Period 1B (Days 8 to 21) has also been corrected throughout the protocol. The protocol has also been amended to make corrections to the text and add further clarification regarding the scientific rationale for study design, justification for dose, dose modification, and withdrawal criteria. Additionally, the exclusion criteria have been updated to exclude study participants with severe renal impairment.

Section # and Name	Description of Change	Brief Rationale
Synopsis Overall design	Corrected timing for Period 1B to Days 8 to 21	Correction
Section 1.3 Schedule of activities	Added recording of adverse events/medical procedures on Day 8	Correction
Section 1.3 Schedule of activities	Clarification of footnotes regarding timing of collection of samples for safety laboratory evaluations, pharmacokinetics, and plasma protein binding	Clarification
Section 1.3 Schedule of activities	Corrected collection of plasma protein binding and urine pharmacokinetics samples from Day 12 to Day 13	Correction
Section 4.1.2 Treatment Period	Corrected timing for Period 1B to Days 8 to 21	Correction
Section 4.2 Scientific rationale for study design	Edited text	Clarification
Section 4.3 Justification for dose	Edited text	Clarification
Section 5.2 Exclusion criteria	Added exclusion criterion #17	To exclude study participants with severe renal impairment

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Preparation, handling, storage, and accountability requirements	Removed the following sentence: The Investigator (or designee) will instruct the study participant to store the study medication following the instructions on the label.	Correction- study medication will be administered in the clinic; therefore, storage instructions for the participant are unnecessary
Section 6.6 Dose modification	Edited text	To align with other padsevonil studies
Section 7.1.2 Criteria for study hold due to adverse events	Section removed	Section is not required because Rapid Alert procedures are not being used in this study
Section 7.2 Participant discontinuation/withdrawal from the study	Added the following withdrawal criterion: There is a confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.	To explicitly state that study participants with a confirmed pregnancy should be removed from the study
Section 7.2 Participant discontinuation/withdrawal from the study	Edited text regarding the replacement of study participants who are withdrawn from the study	To align with other padsevonil protocols
Section 8.2 Plasma protein binding	Edited text	To clarify the reporting of data for plasma protein binding of PSL and its metabolites
Section 10.2 Appendix 2: Clinical laboratory tests	Edited hematology laboratory assessments to include absolute reticulocyte counts instead of % reticulocytes	Correction
Section 10.4.2 Contraception guidance	Edited text to the following: male study participants must refrain from donating sperm for the duration of the study and for 7 days after the final dose of study medication	For consistency with Section 5.2

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**US:** +1 800 880 6949 Or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

An open-label, parallel-group, pharmacokinetic, safety and tolerability study of single and multiple oral administrations of padsevonil in adult and elderly study participants

Short title:

An open-label pharmacokinetic and safety study of single and multiple administrations of padsevonil in adult and elderly study participants.

Rationale:

Padsevonil (PSL) is a novel chemical entity with selective affinity for both presynaptic vesicle protein 2 isoforms and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid (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 P450 (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 in adult study participants with epilepsy. The treatment of focal-onset seizures is often complex and associated with an increased concern for safety and tolerability in the elderly population due to age-related changes altering the pharmacokinetics (PK), disposition, and elimination of antiepileptic medicines (Motika and Spencer, 2016). Thus, the objective of this Phase 1, open-label study is to evaluate the effect of age on PK, safety, and tolerability of single and multiple oral doses of PSL in adult (ages 18 to 64 years) and elderly (≥65 years) study participants. The study will explore any PK, safety, and tolerability differences between the adult and elderly cohort.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the plasma PK of PSL in adult and elderly study participants	• Single dose: C_{max}, AUC_{0-t}, AUC • Multiple dose: $C_{max,ss}$, AUC_{tau}
Secondary	
• To evaluate the urine PK of PSL in adult and elderly study participants	• Amount excreted and metabolic ratio of amount excreted
• To evaluate the safety and tolerability of PSL in adult and elderly study participants	• Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation

Objectives	Endpoints
Other	
• To evaluate the plasma PK of PSL and 2 of its major metabolites [redacted] in adult and elderly study participants	For PSL metabolites: • Single dose: AUC, $AUC_{(0-t)}$, and C_{max} • Multiple dose: AUC_{tau} and $C_{max,ss}$ For PSL and its metabolites: • Single dose: t_{max}, $t_{1/2}$, $AUC_{(0-12)}$ • Multiple dose : t_{max}, $t_{1/2ss}$, C_{trough}, CL/F_{ss}, metabolic ratios of AUC_{tau} and C_{max} For PSL: Bound and unbound plasma concentration of PSL in two samples.
• To evaluate the urine PK of PSL and 2 of its major metabolites [redacted] in adult and elderly study participants	For PSL and its metabolites: • Single and multiple dose: CL_R and f_e
• To evaluate the relationship between creatinine clearance and hepatic function tests and the PK of PSL and 2 of its major metabolites [redacted] in adult and elderly study participants.	For PSL and its metabolites: • Single and multiple dose: regression analysis with AUC, CL/F_{ss}, and CL_R vs age, vs creatinine clearance, bilirubin, AST, and ALT
• To evaluate the safety and tolerability of PSL in adult and elderly study participants	• Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis) • Changes in vital signs (pulse rate, BP, respiratory rate, and body temperature) • Changes in 12-lead ECG assessment • Physical examination findings

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic; PSL=padsevonil; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Overall design

This is a Phase 1, open-label study to evaluate the effect of age on the PK, safety, and tolerability of 200mg oral PSL in 2 cohorts of at least 10 adult (18 to 64 years, inclusive) (Cohort A) and 18 elderly (≥65 years) study participants (Cohort B). The study utilizes a single dose (SD) and a multiple dose (MD) design.

The study consists of Screening, a Baseline Visit, Treatment Period, and Follow-up Period (End-of-Study/End-of-Treatment [EOS/EOT] Visit).

Screening will be conducted at the study site(s) 3 to 28 days prior to check-in to the study site. Eligible study participants in the 2 age cohorts will be matched per gender for body weight if feasible, ie, the elderly study participants will be recruited first, and per gender, matched for body weight with adult study participants. Individual cases will be discussed with the Sponsor as needed. In each age cohort, there will be a homogenous repartition between male and female study participants, with at least 3 participants in each gender. To allow for an investigation of potential age-dependent effects, the elderly study participant cohort will also preferably include the following categories: at least 3 males and 3 females from ≥65 to 74 years old, and at least 3 males and 3 females ≥75 years old.

Study participants will check into the study site on Day -1 for the Baseline Visit and will undergo assessments as specified in the Schedule of Activities (Table 1-2).

The Treatment Period consists of Period 1A (PSL SD administration) on Days 1 to 7 and Period 1B (PSL MD administration) on Days 8 to 21.

In Period 1A, study participants will receive a single oral dose of 200mg PSL on Day 1, at approximately 8:00am, 30 minutes after a light meal. No study drug will be administered on Days 2 to 7; assessments will be conducted during this time as specified in the Schedule of Activities (Table 1-2). Days 2 to 7 are designated as a 6-day washout.

In Period 1B, study participants will receive multiple oral doses of PSL as follows (note: twice daily [BID] dosing is achieved with a morning [approximately 8:00am] and evening [approximately 8:00pm] dose):

- Day 8: 50mg PSL BID
- Day 9: 100mg PSL BID
- Days 10 to 12: 200mg PSL BID
- Day 13: A morning dose of 200mg PSL and an evening dose of 100mg PSL
- Days 14 and 15: 100mg PSL BID
- Day 16: 50mg PSL BID
- Days 17 to 21: no PSL administration; 5-day washout

Throughout the study, plasma and urine samples for PK analysis and safety evaluations will be obtained according to the Schedule of Activities (Table 1-2). Adverse events and concomitant medications will be recorded throughout the study. Liver function parameters and creatinine clearance will be assessed in each study participant. These parameters are influenced by age; therefore, the acceptance ranges for these tests are wider for the elderly study participants.

On Day 22, study participants will complete the EOS/EOT Visit procedures as specified in the Schedule of Activities (Table 1-2).

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

Number of participants

A total of approximately 28 study participants will be enrolled overall in the US (at least 10 adult and at least 18 elderly study participants).

Treatment groups and duration

The maximum study duration for adult and elderly study participants is 50 days (up to 28 days for Screening plus 22 days from Baseline [Day 1] through the EOS/EOT Visit).

1.2 Schema

A schematic of the study design is provided in Table 1-1.

Table 1-1: Study schematic

	Cohort A (adults; n=at least 10) and Cohort B (elderly; n=at least 18)															
	Treatment Period															Follow-up Period
	Period 1A (SD)					Period 1B (MD)										EOS/ EOT Visit
Day	**1**	**2**	**3**	**4**	**5 to 7**	**8**	**9**	**10**	**11**	**12**	**13 morning**	**13 evening**	**14**	**15**	**16**	**17 to 21**	**22**
		Washout														**Washout**	
PSL Dose (mg)	200					50 BID	100 BID	200 BID	200 BID	200 BID	200	100	100 BID	100 BID	50 BID		
	Plasma	Plasma	Plasma	Plasma							Plasma						
	Urine	Urine	Urine	Urine							Urine						

BID=twice daily; EOS=End-of-Study; EOT=End-of-Treatment; MD=multiple dose; PK=pharmacokinetic(s); PSL=padsevonil; SD=single dose
Note: BID dosing will be at approximately 8:00am and 8:00pm.
Note: To allow age-dependent effects, elderly study participants will include preferably the following categories: at least 3 males and 3 females from ≥65 to 74 years old and at least 3 males and 3 females ≥75 years old. The elderly study participants will be analyzed as one group. If an effect of age category is observed on PK or safety parameters, the effect of the age category will be explored.

1.3 Schedule of activities

The schedule of activities is provided in Table 1-2.

Table 1-2: Schedule of activities

Study Period/Visit	Scr	BL Visit	Treatment Period															Follow-up Period
			Period 1A (SD)						Period 1B (MD)									EOS/ EOT Visit
Study Day(s)	**-28 to -3**	**-1**	**1**	**2**	**3**	**4**	**5-7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17-21**	**22**
				Washout													Washout	
Procedures																		
Written Informed Consent	X																	
Demographics & baseline characteristics	X	X																
Inclusion/exclusion criteria verification	X	X																
General medical/procedures history	X	X																
Study Participant Identification Card assigned		X																
Suicidality risk evaluation (C-SRSS) [a]	X	X				X										X		X
Physical examination [b]	X	X	X			X		X								X		X
Psychiatric and Mental Status	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X
Vital signs [c]	X	X	X				X	X	X	X	X	X	X	X	X	X		X
Pregnancy test [d]	X	X																X
Hematology, serum chemistry, urinalysis [e]	X	X				X		X					X			X		X
Serology (HIV, Hep B & C)	X																	
12-lead ECG [f]	X	X	X					X	X	X	X	X	X	X	X	X		
Urine and cotinine drug screen, alcohol breath test	X	X						X										
Recording of AEs /medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-2: Schedule of activities

Study Period/Visit	Scr	BL Visit	Treatment Period															Follow-up Period
			Period 1A (SD)						Period 1B (MD)									EOS/ EOT Visit
Study Day(s)	-28 to -3	-1	1	2	3	4	5-7	8	9	10	11	12	13	14	15	16	17-21	22
			Washout														Washout	
Procedures																		
Admit to study center		X [g]					X [g]											
Discharge from study center							X [g]										X [g]	X
Administer PSL			X					X	X	X	X	X	X	X	X	X		
Study drug accountability			X						X	X	X	X	X	X	X	X		
Blood sampling for PSL PK levels [h]			X	X	X	X							X					
Additional blood sampling for PPB [i]													X					
Urine collection for PSL PK [j]			X	X	X	X							X					
Final disposition determination [k]																		X

AE=adverse event; BID=twice daily; BL=Baseline; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; Hep=hepatitis; HIV=human immunodeficiency virus; MD=multiple dose; PK=pharmacokinetic(s); PPB=plasma protein binding; PSL=padsevonil; Scr=screening; SD=single dose; t_{max}=time to maximum plasma concentration

[a] 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.

[b] At Screening, Baseline (Day -1) and Day 8, a full physical examination will be performed. On all other days a physical examination is performed, it will be a short physical examination (see Section 8.3.4).

[c] Vital signs will be performed before each morning dose of PSL; if feasible; vital sign evaluations will follow the same schedule as ECGs. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the study participant in a quiet setting without distractions (eg, television, cell phones).

[d] Serum pregnancy test will be performed for females of childbearing potential at Screening. Urine pregnancy testing will be performed at all other time points indicated.

[e] For safety laboratory evaluations that occur on a dosing day, these will be performed before the morning dose/PK sample collection.

[f] A 12-lead ECG will be performed after a rest of at least 5 minutes. All ECG recordings will be performed in triplicate at 2 to 3 minute intervals at Screening, Baseline (Day -1), predose and 3 hours after the morning dose on each PSL dosing day and EOS/EOT Visit.

[g] Study participants will be confined to the study site starting at Baseline (Day -1) and may be discharged on the morning of Day 5 after the assessments are complete, per the discretion of the Investigator. Study participants discharged on Day 5 will be readmitted to the study site on the evening of Day 7. If the Investigator deems it acceptable, study participants may be discharged the morning of Day 17.

[h] PK plasma samples will be taken at the following time points: (a) Period 1A (single dose): predose on Day 1 and 0.25, 0.5, 0.75, 1, 1.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose (14 samples); (b) Period 1B (multiple doses): predose (morning dose), and 0.25, 0.5, 0.75, 1, 1.5, 3, 4, 6, 8, and 12h after the morning dose (11 samples).

[i] Two blood samples will be collected after multiple doses at steady state (Day 13 predose and 1.5h postdose[(~t_{max}]) for PPB.

[j] After the morning urine void and collection of a predose sample (no more than 60 minutes before dosing), PK urine collection will be performed at regular intervals on Days 1, 2, 3, and 4 at the following time points: 0 to <12h; 12 to <24h, 24 to <48h, and 48 to <72h after the single dose (4 samples). On Day 13, PK urine collection will be performed 0 to 12h after the 200mg PSL morning dose (1 sample).

[k] For study participants prematurely terminating or completing the study, final disposition is recorded at the EOS/EOT Visit. All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures, in accordance with the EOS/EOT Visit schedule, as soon as possible after the last dose of study medication.

2 INTRODUCTION

2.1 Study rationale

Padsevonil is a novel chemical entity with selective affinity for both presynaptic vesicle protein 2 isoforms and postsynaptic cBZR sites on the 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 CYP pathway; the formation of the 2 major metabolites, [redacted] is mainly mediated by CYP3A4, with potential involvement of CYP2C19.

Padsevonil is currently being investigated in adult study participants with epilepsy. The treatment of focal-onset seizures with anti-epileptic medications is often complex and associated with an increased concern for safety and tolerability in the elderly population (Motika and Spencer, 2016). Both the prevalence and incidence of epilepsy increase in adults over 60 years old, and most new-onset epilepsy seizures are focal and as a result of new neurological conditions. The increase in both comorbid medical conditions and concomitant medications in elderly patients likely leads to an increase in side effects compared with younger patients. Additionally, PK considerations in elderly study participants include a decline in renal function associated with differences in clearance and elimination. Of particular relevance to PSL, an age-related decline in hepatic function is associated with decreased metabolism of CYP activity and a potential increase in serum levels. Moreover, changes in body mass and fat in elderly study participants can alter the disposition of drugs, and changes in serum proteins can result in changes in the drug free fraction and toxicity.

An appropriate representation of the geriatric population (including patients with concomitant therapies and co-morbidities) is recommended to be enrolled in the clinical development program to adequately characterize efficacy and safety in the geriatric population and allow for comparisons with the nongeriatric population (Food and Drug Administration Guidance for Industry, 2012). A separate study in the geriatric population is desired as it is unlikely that sufficient data in elderly study participants (>10%) could be collected from pivotal studies with PSL. Thus, the objective of this Phase 1, open-label study is to evaluate the effect of age on the PK, safety, and tolerability of single and multiple oral doses of PSL in adult (ages 18 to 64 years) and elderly (≥65 years) study participants.

2.2 Background

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

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

Compounds binding to synaptic vesicle protein 2A (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 synaptic vesicle protein 2B (SV2B) and synaptic vesicle protein 2C (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 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 treatment for focal-onset seizures in patients with epilepsy.

2.3 Benefit/risk assessment

Overall, the clinical pharmacology and clinical studies in drug-resistant epilepsy have 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 (CNS) 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) following PSL administration are consistent with adverse effects of other AEDs, including SV2A ligands. Events reported in PSL clinical studies were transient, acute, and required admission to psychiatric care and medical treatment. The events in 2 healthy study participants occurred early after initiation or cessation of

PSL, which was done without titration or tapering. The psychotic effect in an epilepsy study participant emerged after dramatic improvement in seizure control and electroencephalogram activity a few weeks after the start of PSL, suggesting a "forced normalization" (Clemens, 2005; Loganathan et al, 2015). Dose reduction of PSL and medical treatment resulted in complete resolution of psychosis within days as the treatment with PSL continued. The occurrence of acute psychiatric SAEs in these 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 and monitoring of psychiatric and mental status changes.

Despite the occurrence of several electrocardiogram (ECG) findings (including different types of ectopy) following PSL administration 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 Phase 1 or Phase 2 studies and all echocardiograms were assessed as normal. There are currently no data to suggest that PSL 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 posttreatment have been implemented in the studies that have a >3-week treatment duration. To date, no clinically significant echocardiogram findings (only minor/trace or Grade 1 findings) have been observed.

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

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

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the plasma PK of PSL in adult and elderly study participants	• Single dose: C_{max}, AUC_{0-t}, AUC • Multiple dose: $C_{max,ss}$, AUC_{tau}
Secondary	
• To evaluate the urine PK of PSL in adult and elderly study participants	• Amount excreted and metabolic ratio of amount excreted
• To evaluate the safety and tolerability of PSL in adult and elderly study participants	• Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation
Other	
• To evaluate the plasma PK of PSL and 2 of its major metabolites [redacted] in adult and elderly study participants	<u>For PSL metabolites:</u> • Single dose: AUC, $AUC_{(0-t)}$, and C_{max} • Multiple dose: AUC_{tau} and $C_{max,ss}$ <u>For PSL and its metabolites:</u> • Single dose: t_{max}, $t_{1/2}$, $AUC_{(0-12)}$ • Multiple dose : t_{max}, $t_{1/2ss}$, C_{trough}, CL/F_{ss}, metabolic ratios of AUC_{tau} and C_{max} <u>For PSL:</u> Bound and unbound plasma concentration of PSL in two samples.
• To evaluate the urine PK of PSL and 2 of its major metabolites ([redacted]) in adult and elderly study participants	<u>For PSL and its metabolites:</u> • Single and multiple dose: CL_R and f_e
• To evaluate the relationship between creatinine clearance and hepatic function tests and the PK of PSL and 2 of its major metabolites [redacted] in adult and elderly study participants.	<u>For PSL and its metabolites:</u> • Single and multiple dose: regression analysis with AUC, CL/F_{ss}, and CL_R vs age, vs creatinine clearance, bilirubin, AST, and ALT
• To evaluate the safety and tolerability of PSL in adult and elderly study participants	• Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis) • Changes in vital signs (pulse rate, BP, respiratory rate, and body temperature) • Changes in 12-lead ECG assessment

Objectives	Endpoints
	• Physical examination findings

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic; PSL=padsevonil; 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 age on the PK, safety, and tolerability of oral PSL in 2 cohorts of at least 10 adult (18 to 64 years, inclusive) study participants (Cohort A) and 18 elderly (≥65 years) study participants (Cohort B).

The study utilizes a SD and a MD design. Period 1A is the SD Period and consists of a single dose of PSL followed by a Washout Period. Period 1B is the MD Period and consists of PSL up-titration, maintenance, and tapering during the Treatment Period, followed by a Washout Period. Both adult and elderly study participants will take part in the SD and MD Periods.

The total study duration for each study participant is up to 28 days for Screening plus 22 days from Day 1 through the EOS/EOT Visit (up to 50 days in total).

A study schema is provided in Table 1-1 and the Schedule of Activities is provided in Table 1-2.

4.1.1 Screening and Baseline Period

Screening will be conducted at the study site 3 to 28 days prior to check-in to the study site.

Study participants will sign a written informed consent form (ICF) prior to the conduct of any study-related procedures. Screening assessments will be conducted as specified in the Schedule of Activities (Table 1-2), after which the study participants' eligibility will be determined on the basis of the inclusion/exclusion criteria.

Eligible study participants in the 2 age cohorts will be matched per gender for body weight if feasible; ie, the elderly study participants will be recruited first, and per gender, matched for body weight with adult study participants. Individual cases will be discussed with the Sponsor as needed. In each age cohort, there will be a homogenous repartition between male and female study participants, with at least 3 participants in each gender. To allow for an evaluation of potential age-dependent effects, the elderly study participant cohort will also preferably include the following categories: at least 3 males and 3 females from ≥65 to 74 years old, and at least 3 males and 3 females ≥75 years old.

The Baseline Period will begin when study participants check into the study site on Day -1 and undergo Baseline assessments as specified in the Schedule of Activities (Table 1-2). The Investigator will ensure clear instructions are provided on prohibited concomitant foods and medications that must be avoided.

4.1.2 Treatment Period

The Treatment Period consists of Period 1A (PSL SD administration) on Days 1 to 7 and Period 1B (PSL MD administration) on Days 8 to 21.

In Period 1A, study participants will receive a single oral dose of 200mg PSL on Day 1, at approximately 8:00am, 30 minutes after a light meal has finished. No study drug will be administered on Days 2 to 7; assessments will be conducted during this time as specified in the Schedule of Activities (Table 1-2). Days 2 to 7 are designated as a 6-day washout.

In Period 1B, study participants will receive multiple oral PSL doses on Days 8 to 15, followed by a 5-day washout (Days17 to 21). Padsevonil will be administered BID, with one dose in the morning [approximately 8:00am] and one dose in the evening [approximately 8:00pm]. Each morning dose will be administered 30 minutes after a light meal has finished. Each evening dose will be administered 30 minutes after a standard meal has finished. The specific PSL dosing schedule is as follows:

- Day 8: 50mg PSL BID
- Day 9: 100mg PSL BID
- Days 10 to 12: 200mg PSL BID
- Day 13: A morning dose of 200mg PSL and an evening dose of 100mg PSL
- Days 14 and 15: 100mg PSL BID
- Day 16: 50mg PSL BID
- Days 17 to 21: no PSL administration; 5-day washout

Dosing will be stopped in any individual study participant, or across the whole study, if any of the relevant individual or study stopping criteria (detailed in Section 7) are met. Decisions about dosing or study cessation for individual study participants should be discussed first with the UCB Study Physician.

Throughout the study, plasma and urine samples for PK analysis and safety evaluations will be performed according to the Schedule of Activities (Table 1-2). Adverse events and concomitant medications will be recorded throughout the study. Liver function parameters and creatinine clearance will be assessed in each study participant. These parameters are influenced by age; therefore, the acceptance ranges for these tests are wider for the elderly study participants.

Study participants will be admitted to the study site on Day -1 prior to the start of dosing. Per Investigator discretion, study participants may be discharged on the morning of Day 5 through the evening of Day 7. Study participants will be readmitted on the evening of Day 7 and will remain on site until the morning of Day 17, when they may be discharged with the permission of the Investigator.

4.1.3 Follow-up Period

Study participants will return to the study site on Day 22 to complete the Follow-up Period, which consists of the EOS/EOT Visit. At this visit, study participants will complete the EOS/EOT Visit procedures as specified in the Schedule of Activities (Table 1-2), completing their participation in the study.

4.2 Scientific rationale for study design

UP0053 is an initial study to explore the effect of age on PK and safety of PSL in study participants. To evaluate age, the study includes 2 age cohorts: adult (ages 18 to 64 years) and

elderly (≥65 years) study participants. Furthermore, the elderly cohort is planned to include a further age-stratified breakdown of at least 3 males and 3 females from ≥65 to 74 years old and at least 3 males and 3 females ≥75 years old.

To be able to fully characterize the effect of age on PK and safety of PSL, PSL is being administered to the same study participants as both SD (Period 1A) and MD (Period 1B). Multiple dosing of PSL is included in this study because time-dependent inhibition of apparent clearance, resulting in higher PSL exposures, was observed in previous studies, which implies that SD PK cannot be extrapolated linearly to a multiple dose profile.

4.3 Justification for dose

During the SD Period, study participants will receive a single oral dose of 200mg PSL. During the MD Period, study participants will receive 200mg PSL BID, as well as 50mg PSL BID and 100mg PSL BID for titration and tapering. Doses up to 400mg BID, including the 200mg BID dose, are being evaluated in global PSL Phase 2 and Phase 3 clinical studies intended for registration.

A dose of 400mg PSL is considered the maximum tolerated dose (MTD) based on data from Phase 1 studies with PSL. In this study, the planned doses are well under the MTD and consistent with the doses being investigated for PSL registration.

From the tolerability data generated in the PSL Phase 1 and 2 studies, study participants with epilepsy appear to tolerate higher doses of PSL (particularly the MTD of 400mg) compared with healthy study participants. While the reasons for this are not fully clear, PSL has a dual activity at SV2 and GABA-A receptors, and it is assumed that minimizing GABA-A receptor occupancy may increase tolerability. In the Phase 1 studies N01383 and UP0036, it has been demonstrated that 200mg PSL has minimal but quantifiable GABA-A receptor occupancy while also being associated with high and sustained SV2A receptor occupancy.

Padsevonil is predominantly cleared hepatically, and hepatic function as well as renal function decreases with age, which suggests that exposure in elderly study participants might be increased due to a reduced hepatic function. Renal clearance of the parent and the desmethyl-metabolite is <1% of the dose and only approximately 18% of the dose is excreted in the urine as an inactive carboxylic acid metabolite.

Based on the potential differences in the tolerability of PSL in healthy adults and the elderly, and to allow for potential excursions in exposure without encountering tolerability issues at a clinically relevant dose, PSL 200mg BID is the selected dose for this study.

Taking all the above considerations into account, together with the primary and secondary objectives for this study, the PSL 200mg dose is deemed sufficient to evaluate the plasma PK, safety, and tolerability of PSL. It is likely that differences in either PK or safety and tolerability at the PSL 200mg dose can be extrapolated for the PSL 100mg BID and 400mg BID doses to be evaluated in the Phase 3 clinical studies intended for registration. Thus, in summary, the doses were chosen to provide reasonable exposure while optimizing expected tolerability in the healthy adult and elderly study participants because there was no anticipated benefit for the healthy study participants.

4.4 End of study definition

A study 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/EOT Visit in the Schedule of Activities (Table 1-2).

The end of the study is defined as the date of last scheduled procedure shown in the Schedule of Activities (Table 1-2) for the last study participant in the study globally.

The maximum study duration per study participant is 50 days, including up to 28 days for Screening and 22 days on study (ie, from Day 1 through the EOS/EOT Visit).

5 STUDY POPULATION

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

5.1 Inclusion criteria

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

Age

1. Study participants in the adult cohort must be ≥18 to 64 years of age at the time of signing the ICF.
2. Study participants in the elderly cohort must be ≥65 years of age at the time of signing the ICF.

Type of participant and disease characteristics

3. Study participants who are overtly healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, and cardiac monitoring. In addition, elderly study participants must be considered to be in general good physical and mental health.

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

Weight

4. Study participants must have a body weight of at least 50kg for males and 45kg for females, and a body mass index within the range of 18 to 32 kg/m^2 (inclusive).

Sex

5. Male and/or female study participants must meet the following requirements to be included in the study:
   - A male study participant must agree to use contraception as detailed in Appendix 4 [Section 10.4] during the Treatment Period and for at least 7 days after the last dose of study treatment and refrain from donating sperm during this period.
   - A female study participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one 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 the Treatment Period and for at least 90 days after the last dose of study treatment.

Informed consent

6. Study participants 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 ICF and in this protocol.
7. Study participant is considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator, and is capable of communicating satisfactorily with the Investigator.

5.2 Exclusion criteria

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

Medical conditions

1. Study participant has a current or past psychiatric condition that, in the opinion of the Investigator, could compromise the study participant's safety or ability to participate in this study, or a history of schizophrenia or other psychotic disorder, bipolar disorder, or severe unipolar depression. The presence of potential psychiatric exclusion criteria will be determined based on the psychiatric history collected at Screening.
2. Study participant has history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
3. Study participant has a history of chronic alcohol or drug abuse within the previous 6 months. A study 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).
4. Study participant has a positive pre-study drug/alcohol screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines.

Note: A study participant with a positive finding on the alcohol and/or drug screen may still be enrolled at the discretion of the Investigator if a plausible clinical explanation exists (eg, prior or concomitant medication use)

5. Study participant has a known hypersensitivity to any components of the study medication as stated in this protocol.
6. Subject has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
7. Study participant has abnormal blood pressure according to the following:

   Note: This includes both the routine and orthostatic hypotension BP assessments.

   For routine BP, study participants in the adult cohort must have blood pressure and pulse rate within normal range in the supine position after 5 minutes rest (SBP: 90mmHg to 145mmHg; DBP: 40mmHg to 95mmHg; PR: 40bpm to 100bpm).

   Study participants in the elderly cohort must have BP and pulse rate within normal range in the supine position after 5 minutes of rest (SBP: 90mmHg to 170mmHg; DBP: 40mmHg to 100mmHg; pulse rate: 40bpm to 110bpm).

   Any values marginally (ie, no more than 5mmHg) outside the normal range but considered not clinically significant by the Investigator are allowed. In the case of an out-of-range result, 1 repeat will be allowed. If the readings are out of range again, the study participant will not be included.
8. Study 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.

Suicidality

9. Study participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has had suicidal ideation in the past 6 months as indicated by a positive response (“Yes”) to either Question 4 or Question 5 of the “Screening/Baseline” version of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Prior/Concomitant therapy

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

Prior/Concurrent clinical study experience

12. Study participant has previously received PSL in this or another study.

13. Study participant has participated in another study of an investigational medicinal product (IMP) (and/or an investigational device) within the previous 30 days before Screening (or within 5 half-lives for the IMP, whichever is longer) or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

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

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

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.
17. Study participant has severe renal impairment as indicated by an estimated glomerular filtration rate (GFR)<30mL/min, calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 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] x 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
18. Study participant has any clinically relevant ECG finding at Screening or at Baseline. Study participant has an abnormality in the 12-lead ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett's formula (QTcB) or Fridericia's formula (QTcF) >450ms in study participants in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval ≥220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out of range result, 1 repeat will be allowed. If out of range again, the study participant cannot be included.

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

NOTE B: The specific formula used to determine eligibility and discontinuation for an individual study participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual study participant and then the lowest QTc value used to include or discontinue the study participant.

19. Study participant has the presence of hepatitis B surface antigen at Screening or within 3 months prior to dosing.
20. Study participant has a positive hepatitis C antibody test result at screening or within 3 months prior to starting IP.

    NOTE: Study participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative Hepatitis C ribonucleic acid test is obtained.
21. Study participant has a positive human immunodeficiency virus antibody test.

Other exclusions

22. Study participant has made a blood or plasma donation or has had a comparable blood loss (>450mL) within the last 30 days prior to the Screening Visit. Blood donation during the study is not permitted.
23. Study participant has a consumption of more than 600mg of caffeine/day (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg).
24. Study participant smokes more than 5 cigarettes per day (or equivalent) or has done so within 6 months prior to Screening. Smoking within 48 hours prior to CNS assessments is prohibited.
25. Study participant ingests grapefruit (as beverage, fruit, or supplements) within 72 hours before each administration of study medication. If this is the case at the start of the study, study participants may be rescreened.
26. Female study participant tests positive for pregnancy, plans to get pregnant during participation in the study, or is breastfeeding.
27. Study participant has a diet that deviates notably from the "normal" amounts of protein, carbohydrate, and fat, as judged by the Investigator.
28. Study participant has undergone sudden and/or extreme changes in exercise levels for 2 weeks prior to Screening.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Study participants must refrain from consumption of grapefruit, starfruit, and pawpaw (as beverage, fruit or supplements) from 72 hours before the start of study treatment until after the final dose.
- Study 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. 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.
- Study participants will take PSL orally with 8oz (240mL) water. The use of beverages between 1h predose and 2h postdose should be limited to a maximum of 100mL (in order to keep groups comparable with respect to period of dosing). Water will be available ad libitum except for between 1 hour before and 2 hours after dosing.

5.3.2 Caffeine, alcohol, and tobacco

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

5.4 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure study participants to meet the Consolidated Standards of Reporting Trials 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 (ie, screen failures) 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 meet the exclusion 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.

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.

Rescreened study participants should be assigned a new study participant number.

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

6 STUDY TREATMENTS

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

6.1 Treatments administered

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

Table 6-1: Treatment administered

Study Treatment Name:	**PSL**
Dosage formulation:	Tablets
Unit dose strength(s)/Dosage level(s):	25mg and 100mg strength for QD and BID dosing
Route of administration:	Oral
Dosing instructions:	All treatments will be administered orally with 8oz. (240mL) water. The use of beverages between 1h predose and 2h postdose should be limited to a maximum of 100mL (in order to keep groups comparable with respect to period of dosing). Study participants will complete a light meal 30 minutes prior to each morning dose of PSL and will complete a standard meal 30 minutes prior to the evening dose of PSL. Treatments will be administered in an open-label fashion. Study participants will be dosed in an upright position and will remain semi-recumbent until 4h afterwards.
Packaging and labeling:	Padsevonil tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.
Manufacturer:	UCB

BID=twice per day; PSL=padsevonil; QD=once per day

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

Only study participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

Further guidance and information for the final disposition of unused study treatment are provided in the UP0053 IMP Handling Manual.

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

Randomization and blinding are not applicable for this open-label study.

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

6.3.1 Procedures for maintaining and breaking the treatment blind

Not applicable.

6.4 Treatment compliance

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

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- For elderly study participants with stable conditions, use of chronic medication not interfering with the endpoints of the study and at the discretion of the UCB Medical Monitor will be permitted.
- Paracetamol for the treatment of mild symptoms (eg, headache or other pain), given at most every 6 to 8h, not exceeding 2g/day, and with a total of no more than 5g over 7 days
- Inhaled corticosteroids for seasonal rhinitis
- Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy (HRT) or implants, patches, or intrauterine devices/intrauterine hormone-releasing systems delivering progesterone (for female study participants)

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 Medical Monitor should be consulted.
- Drugs of unknown half-lives are prohibited within 2 weeks before administration of PSL and during the clinical part of the study, unless required to treat an AE.

If a study participant needs or takes any prohibited medication, the Investigator will (where possible) discuss with the UCB Medical Monitor 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 continued study participant care or treatment after the end of the study.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

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

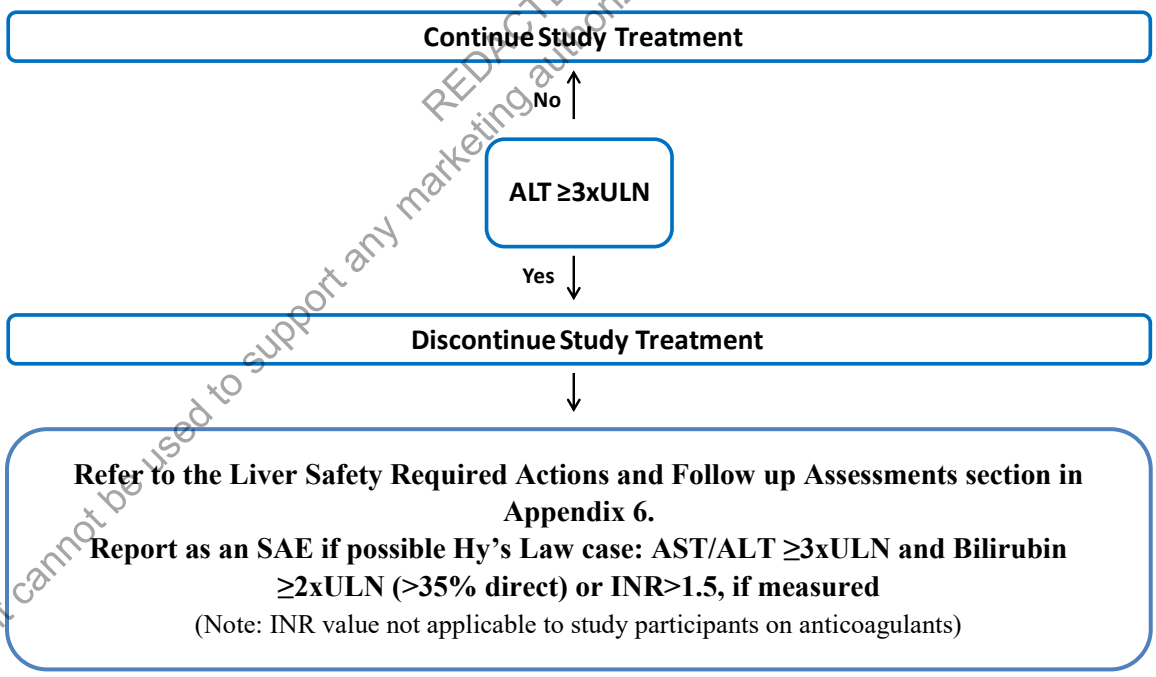
In all cases, the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB Study Physician. If a study participant discontinues study medication, no restart will be allowed.

7.1.1 Liver chemistry stopping criteria

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

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

Figure 7-1: Liver Chemistry Stopping Algorithm



Abbreviations: ALT=alanine 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 are provided in Appendix 6 (Section 10.6).

7.2 Participant discontinuation/withdrawal from the study

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

A study participant may withdraw from the study at any time at his/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 study participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/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 1-2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

1. The study participant develops a clinically relevant medical condition (physical or psychiatric) that, in the opinion of the Investigator, jeopardizes or compromises the study participant's ability to participate in the study or makes it unsafe to continue.
2. The study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. The study participant takes prohibited concomitant medications as defined in this protocol.
4. The study participant withdraws his or her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requests withdrawal of the study participant.
7. The study participant has changes in the ECG that are regarded as clinically significant and/or that worsens 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 judgement 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.

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

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

7.3 Lost to follow up

A study 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 study participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible and counsel the study participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the study participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the study participant (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the study participant continue to be unreachable, he/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 1-2).

Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 1-2), is essential and required for study conduct.

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

Procedures conducted as part of the study participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Table 1-2).

The maximum amount of blood collected from each study participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL. 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 1-2) 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 (24 hour 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.

Genetic analyses will not be performed on these samples unless consent for this was included in the ICF. Study participant confidentiality will be maintained. At visits during which plasma and urine samples for the determination of multiple aspects of PSL will be taken, 1 sample of sufficient volume can be used.

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 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 and urine 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
0.25 to 1.5 hours	2 minutes
2 to 8 hours	5 minutes
12 hours	15 minutes
24 to 48 hours	60 minutes

PK=pharmacokinetic

8.2 Plasma protein binding

Selected plasma samples (described in the Schedule of Activities [Section 1.3]) will be collected and archived to measure the ex-vivo plasma protein binding of PSL and if feasible its metabolites [redacted]. If these investigations are performed, they will be described and reported as an attachment to the clinical study report (CSR).

8.3 Safety assessments

The safety and tolerability of SD and MD of PSL will be monitored by evaluation of AEs, clinical laboratory test results, vital signs (pulse rate, respiratory rate, SBP, DBP, and body temperature), 12-lead ECG parameters, Psychiatric and Mental Status and physical examination findings, and suicidal risk monitoring.

Planned time points for all safety assessments are provided in the Schedule of Activities (Table 1-2).

8.3.1 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-2) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are laboratory findings that change considerably or their frequency or intensity increases more than expected as compared to 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 EOT/EOS Visit should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

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

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the Schedule of Activities (Table 1-2).

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

8.3.2 Vital signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed as outlined in the Schedule of Activities (Table 1-2).

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

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

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

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

8.3.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of Activities (Table 1-2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

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

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.3.4 Physical examination

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

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

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

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

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

8.3.5 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" version of the C-SSRS at Visit 1 (assessing the past 6 months) and the "Baseline" Version of the C-SSRS at Visit 2, followed by the "Since Last Visit" version at the visits indicated on the Schedule of Activities (Table 1-2).

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

8.3.6 Psychiatric and Mental Status

The psychiatric and mental status of participating subjects will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. The Psychiatric and Mental Status assessment will be performed at Baseline and all scheduled time points in the Schedule of Activities (Table 1-2). 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.

8.4 Adverse events

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

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the study participant to discontinue the PSL or UP0053 (see Section 7).

8.4.1 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 1-2).

Medical occurrences that begin before the start of study treatment 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 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.4.2 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 study participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (AESIs) (as defined in Section 8.4.6) will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.4.4 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 study participants and the safety of a study treatment 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 treatment 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8.4.5 Pregnancy

Details of all pregnancies in female study participants and, if indicated, female partners of male study participants, will be collected after the start of study treatment and until 30 days after the birth for any significant medical issues. In certain circumstances, the Sponsor may request that follow up is continued for a period longer than 30 days. If the study participants is lost to follow up and/or refuses to give information, written documentation of attempts to contact the study participant needs to be provided by the Investigator and filed at the site. The Sponsor's Patient Safety (PS) department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

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

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

- The study participant should return for the EOS/EOT Visit.
- The study participant should immediately stop the intake of the study medication or be tapered as instructed at the EOS/EOT Visit.

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

8.4.6 Adverse events of special interest

An AESI 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 AESIs 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 the Sponsor as an AESI (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

8.5 Safety signal detection

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

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

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

8.6 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 Medical Monitor immediately.
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities until study treatment 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 treatment if requested by the UCB Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.7 Efficacy assessments

Efficacy is not evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Genetics

Genetics are not evaluated in this study.

8.10 Medical resource utilization and health economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11 Biomarkers

Biomarkers are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set: All study participants who signed the ICF.
- Full analysis Set (FAS): All enrolled study participants who signed the ICF and received at least one dose of study medication.
- Pharmacokinetic Per Protocol Set (PK-PPS): PK-PPS is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PK parameters and had a sufficient number of samples available to determine at least 1 PK parameter.

9.2 General statistical considerations

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

For continuous variables, summary statistics will include number of study participants, mean, median, standard deviation, minimum, and maximum (geometric mean and geometric coefficient of variation 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 and urine concentration and PK parameters will be presented using 3 significant digits.

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

9.3 Planned safety and other analyses

9.3.1 Pharmacokinetic analyses

Pharmacokinetics 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 2 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 2 major metabolites [redacted] will be summarized by age group (adult [18-64 years] and elderly study participants [≥65 years]) and treatment period using descriptive statistics. If PK effects by age group are observed (ie, between adult and elderly study participants), subgroup analyses may be performed within the elderly age group (age [≥65 to 74 years old and ≥75 years old] and gender).

Individual plasma PSL and its major 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 SD and MD periods of the study, primary PK parameters (AUC and C_{max}) will be assessed in adults and elderly study participants with analysis of variance (ANOVA). Point

estimates for the ratio of geometric means between adults and elderly study participants (and per category, if deemed necessary), 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. Interparticipant variability on PK parameters will be derived from these analyses.

The relationship between PK parameters of PSL (and metabolites) and creatinine clearance, age (numerical), hepatic laboratory parameters (eg, bilirubin, ALT, and AST) will be evaluated using a graphical approach or correlation and linear regression techniques.

9.3.2 Safety analyses

All safety analyses will be performed using the FAS. All safety variables will be summarized by the age group (adult and elderly study participants) and Treatment Period (SD, MD, and overall).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/preferred term and by age group and Treatment Period. The occurrence and incidence of TEAEs will also be summarized by intensity and by relationship to the study medication. Treatment-emergent AEs leading to discontinuation and SAEs will also be summarized.

Laboratory variables and changes from Baseline will be summarized by descriptive statistics at each time point by age group and Treatment Period. Shift tables from Baseline to each post-Baseline time point will be presented by Treatment Period. Values outside the reference range will be flagged in the listings.

Vital sign variables (BP and PR, body temperature, and respiration rate) and changes from Baseline (pre-dose of each Treatment Period) will be summarized by descriptive statistics at each time point by age group and Treatment Period.

Electrocardiogram parameters will be recorded three times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The raw parameters and change from Baseline will be summarized by descriptive statistics at each time point by age group and Treatment Period.

Physical examination abnormalities will be listed.

9.4 Planned efficacy/outcome analyses

Not applicable.

9.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant. Study participants with an important protocol deviation will be excluded from the FAS. Study participants will be excluded from 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 captured in the Important Protocol Deviations document. 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 may be replaced following discussion between 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 formal interim analyses are planned. Details about the safety analyses will be provided in the Safety Monitoring Committee Charter.

9.8 Determination of sample size

No formal sample size computation has been performed for this study. This PK study will be a study of limited size conducted under SD and steady-state conditions to look for sizable differences between adult (18 to 64 years of age) and elderly (≥65 years of age) study participants. A total of 28 study participants (10 study participants age 18 to 64 years and 18 study participants age ≥65 years) is planned.

A sample size of 9 study participants in each age group will have 97% power to detect a fold change in means (expected ratio) of 2.0, assuming that the coefficient of variation is 40% using a 2 group t-test with a 0.05 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 (ICH)-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/Sponsor 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/Sponsor will forward copies of the protocol, ICF, IB,

Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

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

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

Prior to participation in the study, the ICF should be signed and personally dated by the study participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The study participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process,

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

10.1.4 Data protection

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

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

The study participant must be informed that his/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 study participant.

The study 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, and by inspectors from regulatory authorities.

10.1.5 Committees structure

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

10.1.6 Data quality assurance

All study participant data relating to the study will be recorded on the 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 CRF.

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

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

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

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

All essential documents are to be retained by the Investigator until 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/investigational device. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (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 eCRF 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 CRF 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 study participant's source documents.

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

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

10.1.8 Study and site closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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 study participants by the Investigator
- Discontinuation of further study medication development

10.1.9 Publication policy

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

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

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

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 5.1 and Section 7, respectively.
- Additional laboratory tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology[1]</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
Reticulocytes</td><td>WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry[1]</td><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose (fasting at Screening)</td><td>Calcium</td><td>Alkaline phosphatase</td><td></td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• 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.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)
• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
• Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab)
The results of each test must be entered into the eCRF.</td></tr>
</table>

Laboratory Assessments	Parameters
NOTES: [1] 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, respectively. All events of ALT ≥3×UL) and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).	

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 study participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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).

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 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 study participant's medical records to UCB in lieu of completion of the UCB/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the study participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/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 study participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a study participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to 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 study 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 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 study 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 study participants must refrain from donating sperm for the duration of the study and for 7 days after the final dose of study medication.

Male 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 90 days after the final dose of study medication.

10.4.2.2 Pregnancy testing

- Women of childbearing potential 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 Baseline and on Day 11 of the MD Treatment Period. 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 study 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 study participant.

10.4.2.3.2 Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male study participants who receive study medication.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be 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 study 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 study participant's pregnancy. The study participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the study 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 8.4.5. 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 study participant who becomes pregnant while participating in the study will discontinue study medication or be withdrawn from the study.

10.5 Appendix 5: Genetics

Not applicable.

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

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

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants with potential drug-induced liver injury should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or study participant withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for discontinuation of study medication.

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

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

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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT≥3xULN If ALT ≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin) OR international normalized ratio (INR) >1.5, report as a serious adverse event (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 study 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	• Viral hepatitis serology[c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum creatine phosphokinase and lactate dehydrogenase • 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

phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor study 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 study participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• 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. **<u>If</u> ALT ≥3xULN AND <u>bilirubin</u> ≥2xULN <u>or INR</u> >1.5<u>:</u>** • 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 assay (quantifies potential acetaminophen contribution to liver injury in study participants with definite or likely acetaminophen use in the preceding week [James et al, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs.

[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 impairment or cirrhosis). The INR measurement is not required and the stated threshold value will not apply to study participants receiving anticoagulants.

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

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

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
cBZR	central benzodiazepine receptor
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CNS	central nervous system
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report form
EOS	End-of-study
EOT	End-of-treatment
FAS	full analysis set
FSH	follicle stimulating hormone
GABA-A	gamma-aminobutyric acid
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HCG	human chorionic gonadotropin
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
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
MD	multiple dose
MTD	maximum tolerated dose
PK	pharmacokinetic(s)
PK-PPS	pharmacokinetic per protocol set
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	single dose
SV2A	synaptic vesicle protein 2A
SV2B	synaptic vesicle protein 2B
SV2C	synaptic vesicle protein 2C
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 (29 May 2019)

Overall Rationale for the Amendment

The protocol has been amended to provide clarification regarding the collection of samples for safety laboratory evaluations, pharmacokinetics, and plasma protein binding. The timing was corrected for the collection of the samples for plasma protein binding and urine pharmacokinetics. The timing for Period 1B (Days 8 to 21) has also been corrected throughout the protocol. The protocol has also been amended to make corrections to the text and add further clarification regarding the scientific rationale for study design, justification for dose, dose modification, and withdrawal criteria. Additionally, the exclusion criteria have been updated to exclude study participants with severe renal impairment.

Section # and Name	Description of Change	Brief Rationale
Synopsis Overall design	Corrected timing for Period 1B to Days 8 to 21	Correction
Section 1.3 Schedule of activities	Added recording of adverse events/medical procedures on Day 8	Correction
Section 1.3 Schedule of activities	Clarification of footnotes regarding timing of collection of samples for safety laboratory evaluations, pharmacokinetics, and plasma protein binding	Clarification
Section 1.3 Schedule of activities	Corrected collection of plasma protein binding and urine pharmacokinetics samples from Day 12 to Day 13	Correction
Section 4.1.2 Treatment Period	Corrected timing for Period 1B to Days 8 to 21	Correction
Section 4.2 Scientific rationale for study design	Edited text	Clarification
Section 4.3 Justification for dose	Edited text	Clarification
Section 5.2 Exclusion criteria	Added exclusion criterion #17	To exclude study participants with severe renal impairment
Section 6.2 Preparation, handling, storage, and accountability requirements	Removed the following sentence: The Investigator (or designee) will instruct the study participant to store the study medication following the instructions on the label.	Correction- study medication will be administered in the clinic; therefore, storage instructions for the participant are unnecessary

Section # and Name	Description of Change	Brief Rationale
Section 6.6 Dose modification	Edited text	To align with other padsevonil studies
Section 7.1.2 Criteria for study hold due to adverse events	Section removed	Section is not required because Rapid Alert procedures are not being used in this study
Section 7.2 Participant discontinuation/withdrawal from the study	Added the following withdrawal criterion: There is a confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.	To explicitly state that study participants with a confirmed pregnancy should be removed from the study
Section 7.2 Participant discontinuation/withdrawal from the study	Edited text regarding the replacement of study participants who are withdrawn from the study	To align with other padsevonil protocols
Section 8.2 Plasma protein binding	Edited text	To clarify the reporting of data for plasma protein binding of PSL and its metabolites
Section 10.2 Appendix 2: Clinical laboratory tests	Edited hematology laboratory assessments to include absolute reticulocyte counts instead of % reticulocytes	Correction
Section 10.4.2 Contraception guidance	Edited text to the following: male study participants must refrain from donating sperm for the duration of the study and for 7 days after the final dose of study medication	For consistency with Section 5.2

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SPONSOR DECLARATION

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

Approval Signatures

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