A SINGLE-CENTER, RANDOMIZED, PLACEBO-CONTROLLED, 3 TREATMENT PERIOD CROSSOVER STUDY TO ASSESS THE EFFECT OF PADSEVONIL ON CARDIAC REPOLARIZATION (QTc INTERVAL) (USING MOXIFLOXACIN AS A POSITIVE CONTROL) IN HEALTHY STUDY PARTICIPANTS

PROTOCOL UP0050 AMENDMENT 1

PHASE 1

SHORT TITLE:

A placebo-controlled safety and tolerability study comparing the pharmacodynamic effect of high-dose padsevonil on cardiac repolarization, including moxifloxacin as a positive pharmacologic control, in healthy study participants.

Sponsor:
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Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 1	10 Oct 2019	Substantial
Original Protocol	22 Jul 2019	Not applicable

Amendment 1 (10 Oct 2019)

Overall Rationale for the Amendment

The protocol has been amended to comply with the requirement of the Medicines and Healthcare products Regulatory Agency (MHRA). Changes were made in the exclusion criteria to set the upper limit of acceptable range of total bilirubin test results and to clarify language regarding liver function tests (absolute rule for liver function test parameters) for alignment with regulatory requests in another padsevonil (PSL) protocol. Changes were made in Section 7.1.3 (Criteria for study hold due to adverse events) to comply with an MHRA requirement to align with European Medicines Agency Guidance on risk mitigation in first-in-human and early clinical trials. In addition, further changes have been made to correct various other typographical errors and to add clarifying language.

Section # and Name	Description of Change	Brief Rationale
Section 3 Table 3-1	Language regarding a secondary endpoint was removed.	This is a correction to align information in the objective and endpoints section of the summary along with the information in the Schedule of activities (Table 1-1).
Section 5.2-Exclusion Criteria	Changed exclusion criterion #15 to include that isolated bilirubin must be <1.5x upper limit of normal (ULN) instead of >1xULN. Exclusion criterion #15 had the note removed regarding liver function test values above the ULN and repeat tests that could be performed in such situations. Language regarding retesting of participants with out-of-range laboratory values remains elsewhere in the protocol including Section 5.4.1 (Rescreening).	Update exclusion criteria
Section 5.2-Exclusion Criteria	The exception of asymptomatic gallstones was removed from exclusion criterion #16.	Update exclusion criteria
Section 6.1 Table 6-1 Treatments administered	The manufacturer of moxifloxacin has been updated from Bayer to Accord Healthcare, Ltd.	Correction

Section # and Name	Description of Change	Brief Rationale
Section 7.1.3 Criteria for study hold due to adverse events	The criteria have been amended to align with the European Medicines Agency Guidance on risk mitigation in first-in-human and early clinical trials.	Regulatory alignment
Section 8.5.5 Pregnancy	The pregnancy language was updated that UCB will collect pregnancy and birth information for up to 12 months after a birth. This aligns with other PSL protocols.	Correction and alignment with other PSL protocols

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24 hour)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21
Email	**Global:** DS_ICT@ucb.com or DSICT.-@ucb.com

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A single-center, randomized, placebo-controlled, 3 treatment period crossover study to assess the effect of padsevonil on cardiac repolarization (QT interval corrected [QTc]) (using moxifloxacin as a positive control) in healthy study participants.

Short title:

A placebo-controlled safety and tolerability study comparing the pharmacodynamics (PD) effect of high-dose PSL on cardiac repolarization, including moxifloxacin as a positive pharmacologic control, in healthy study participants.

Rationale:

Padsevonil is a novel chemical entity with selective affinity for both presynaptic vesicle protein 2 (SV2) isoforms and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid-A ($GABA_A$) receptor that has shown broad-range efficacy in several preclinical models of epilepsy conducted by UCB.

As is the case with all new chemical entities under development, the development program for PSL as an adjunctive treatment for focal-onset seizures in patients with epilepsy calls for the evaluation of its potential to affect cardiac repolarization, as indicated by prolongation of the heart rate (HR)-corrected QT interval on a standard 12-lead electrocardiogram (ECG).

Historically, such evaluations have been performed (in compliance with International Council for Harmonisation [ICH] Guideline E14, 2005) in large, rigorously controlled clinical studies, across a wide range of target drug exposure (C_{max}) levels that clearly bracket those to be anticipated in patients receiving the drug within the dosing regimen sought in the intended labelling. Use of placebo and a positive control have also usually been mandatory in such 'Thorough' QT (TQT) studies.

However, in response to questions about the potential use of concentration-response analysis ('pharmacokinetic [PK]/PD modeling'), Revision 3 of the E14 Guidance (2017) provided clarification that such an analysis using adequate data from standard early phase clinical studies could provide the necessary evidence in place of a specific TQT study, if certain technical requirements were met.

UCB Pharma, having undertaken a detailed assessment of the data available from the early phase study program with PSL, believes those data to be sufficient to provide an acceptable evaluation across the C_{max} range associated with the anticipated labelled doses and lower, but not at the higher, supratherapeutic levels usually required by E14. The purpose of this study is, therefore, to gather data at the highest dose anticipated in labelling, 400mg twice daily dosing (bid) (which is also the maximum tolerated dose [MTD] for PSL) in comparison to both placebo and a 400mg moxifloxacin positive control (a drug known to have a prolongation effect on the QTc interval), to complete the dataset required.

This is a Phase 1, single-center, randomized, placebo-controlled, 3 treatment period crossover study to assess the effect of PSL on QTc (using moxifloxacin as a positive control) in healthy study participants.

Objectives and endpoints:

Objectives	Endpoints
Primary	
The primary PD objective is: • To evaluate the effects on cardiac repolarization (QTc interval) of high-dose PSL in comparison to placebo in healthy study participants	The primary PD endpoint is: • Placebo-corrected change from Baseline in QTc, based on Fridericia's correction (QTcF) method (ΔΔQTcF) evaluated during the Target Dose Day of the PSL and Placebo Treatment Periods, using time point analysis
Secondary	
The secondary PD objective is: • To evaluate other aspects of the effects on cardiac function of high-dose PSL in comparison with placebo and moxifloxacin	The secondary PD endpoints are: • Placebo-corrected change from Baseline in QTcF after a single dose of moxifloxacin • Placebo-corrected changes from Baseline for HR, PR interval, and QRS interval • Frequency of treatment-emergent changes for T-wave morphology and U-wave presence • Change from Baseline in QTcF (ΔQTcF) evaluated at drug-specific t_{max} (Δt_{max}) for PSL, [redacted], and possibly moxifloxacin
The secondary PK objective is: • To evaluate the plasma PK of PSL at steady state in healthy study participants	The secondary PK endpoints are: • $C_{max,ss}$, t_{max}, and AUC_{τ}, obtained from the plasma concentration-time profiles for PSL at steady state (on the Target Dose Day)
The secondary safety objective is: • To evaluate the safety and tolerability of PSL at the dosed level in healthy study participants	The secondary safety endpoints are: • Adverse events (AEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation of the study

Objectives	Endpoints
Other	
The other PD objectives are: • To evaluate other aspects of the effects on cardiac function of high-dose PSL in comparison with placebo and moxifloxacin • To evaluate (using concentration-QT [C-QT] effect modeling) the relationship between QTc interval and the concentration of PSL and its metabolites	The other PD endpoints are: • Categorical outliers for HR, QTcF, PR interval, and QRS interval • Relationship between ΔQTcF (change from Baseline in QTcF) and the plasma concentrations of PSL, [redacted] and possibly moxifloxacin
The other PK objectives (depending on the outcome of PK and/or QT analyses) are: • To evaluate from plasma samples the PK of PSL and the major metabolites of PSL ([redacted]) • To evaluate from banked plasma samples the PK of moxifloxacin (if needed) in healthy study participants • To collect and store blood for potential absorption, distribution, metabolism, and excretion (ADME) genotyping (if needed)	The other PK endpoints are: • For PSL: – Single dose: AUC_{0-12}, C_{max}, and t_{max}. – Multiple dose: $CL_{ss/F}$ and C_{trough} • For PSL metabolites: – Single dose: AUC_{0-12}, C_{max}, t_{max}, and metabolic ratios for C_{max} and AUC_{0-12} – Multiple dose: AUC_{τ}, AUC_{0-t}, C_{trough}, $C_{max,ss}$, t_{max}, and metabolic ratios for $C_{max,ss}$ and AUC_{τ} • For moxifloxacin (if needed): – Single dose: AUC, AUC_{0-t}, $t_{½}$, $C_{max,}$ and t_{max} • Possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL and metabolite PK analyses) (if needed)
The other safety objective is: • To evaluate safety and tolerability of PSL at the dosed level in healthy study participants	The other safety endpoints are: • Changes from Baseline in safety laboratory data (hematology, clinical chemistry, and urinalysis) • Changes from Baseline in vital signs (pulse rate [PR], respiratory rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) • Changes from Baseline in 12-lead ECG assessment • Physical examination findings

Overall design:

This is a Phase 1, single-center, randomized, placebo-controlled, crossover study of the effects of high-dose PSL (400mg bid at steady state = MTD) on cardiac repolarization, including moxifloxacin as an open-label positive pharmacologic control in healthy study participants.

The study includes a Screening Period (up to 28 days), 3 Treatment Periods, 2 Washout Periods, and the Safety Follow-up (SFU) Period. However, this may vary according to the scheduling of Treatment Periods.

Study participants who provide written informed consent will be screened within 28 days before the first Treatment Period.

During each Treatment Period, each study participant will check into the clinic the day prior to the relevant First Dosing Day. Throughout the relevant Dosing Days, continuous Holter monitoring will be undertaken to provide extracted ECG records at the relevant time points necessary for the evaluation of QT interval effects. During the hour prior to administration of the first dose of each Treatment Period, 3 triplicate ECGs extracted from the Holter record will serve to provide a time-averaged Baseline for that Treatment Period.

For study participants in the PSL Treatment Period, the bid doses of PSL will be titrated up (from PSL 100mg to 400mg) to reach steady state in time for the target dose on the 'Target Dose Day' (Day 8). For further detail on the dose titration, refer to Figure 1-1.

During the first dosing day of each Treatment Period, Holter monitoring will take place from 1 hour prior to the first dose of study medication until dosing (at -0.75, -0.5, and -0.25 hours), and a venous blood sample and vital signs will be collected at the time points specified in the Schedule of activities (Table 1-1).

During the Target Dose Day for each Treatment Period (Day 8), Holter monitoring will take place ≥1 hour prior to the morning dose of study medication until 24 hours following the morning dose (and collection of the Day 9 trough PK sample), and venous blood samples and vital signs will be collected at the time points specified in the Schedule of activities (Table 1-1).

On the evening of each Target Dose Day, all study participants will receive a placebo medication in order to protect the 18- and 24-hour PK/QT evaluations during the PSL Treatment Period.

On Days 12, 13, and 14 of each Treatment Period, study participants will remain at the clinic for inpatient follow-up assessments.

Following completion of each Treatment Period, study participants will be discharged from the clinic, returning on the day prior to the First Dosing Day of the next Treatment Period for readmission. The interval between Treatment Periods (Washout Period) will be sufficient to ensure a minimum of 7 days' washout from the study medication administered during the previous Treatment Period.

Following completion of the final Treatment Period, study participants will be discharged and return for an SFU Visit within 7 to 10 days after their discharge from the clinic.

For further information, see the Schedule of activities (Table 1-1).

Number of participants:

Up to 54 eligible study participants will be randomized.

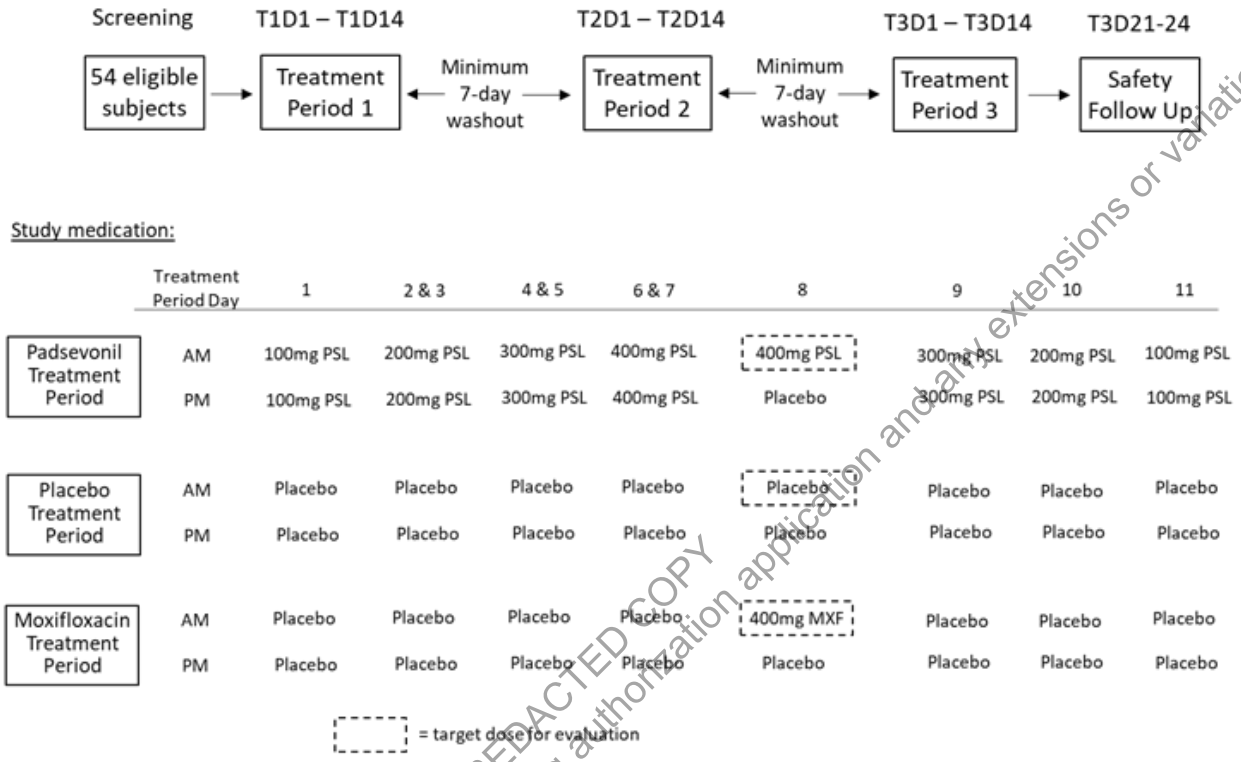
Treatment groups and duration:

The maximum study duration for each study participant will be up to 87 days, including Screening (up to 28 days), crossover dosing across 3 Treatment Periods (14 days per Treatment Period), 2 Washout Periods (7 days per Washout Period), and the SFU Visit (Days 21 to 24).

1.2 Schema

The study design is presented in Figure 1-1.

Figure 1-1: UP0050 Study Design



AM=morning; BID=twice daily; D=Day; MXF=moxifloxacin; PBO=placebo; PM=afternoon; PSL=padsevonil; T=Treatment Period

1.3 Schedule of activities

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

Table 1-1: Schedule of activities

Study Period	SCR	Treatment Periods 1, 2, and 3														SFU/ EOS
		Baseline	Dosing Day											Inpatient FU Days		
Study Day	D -28 to -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	T3 D21-D24
Informed consent	X																
Confirmation of eligibility[a]		X															
Drug screen and alcohol breath testing	X	X															
Admission to clinic		X															
Medical history	X	X	X														
Previous/ concomitant medications	X	X															
PE and neurological examinations	X	X	X													X	X
Body weight/ height[b]	X																
Psychiatric and mental status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-1: Schedule of activities

Study Period	SCR	Treatment Periods 1, 2, and 3														SFU/ EOS
		Baseline	Dosing Day											Inpatient FU Days		
Study Day	D -28 to -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	T3 D21-D24
Suicidality risk assessment (C-SSRS)[c]	X	X														X	X
Hematology, chemistry, urine, serology[d]	X	X														X	X
Pregnancy test[e]	X	X															X
FSH test[f]	X																
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-h Holter monitoring[i]	X		X							X							
Standardized breakfast[j]				X	X	X	X	X	X		X	X	X				
Study medication administration			X	X	X	X	X	X	X	X	X	X	X				
PK sampling			X[k]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[k]	X[l]	X[l]	X[l]	X[l]			
Sampling for ADME genotype analysis			X[m]														
AE inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from clinic																X	

Table 1-1: Schedule of activities

Study Period	SCR	Treatment Periods 1, 2, and 3														SFU/ EOS
		Baseline	Dosing Day											Inpatient FU Days		
Study Day	D -28 to -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	T3 D21-D24

AE=adverse event; BP=blood pressure; C-SSRS=Columbia Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; FSH=follicle stimulating hormone; FU=Follow-up; h=hour; PE=physical exam; PK=pharmacokinetic; SCR=Screening Period; SFU=Safety Follow-up; T=Treatment Period

[a] At the first Baseline Day (D -1) only.

[b] Height will be measured only at Screening. Body weight will be measured at Screening and Baseline (D-1) for each Treatment Period.

[c] Study participants will complete the "Screening/Baseline" version of the C-SSRS during Screening or Baseline (D-1) visits, followed by the "Since Last Visit" version at subsequent visits.

[d] Virus serology will be measured only at Screening. All laboratory blood assessments may be performed nonfasting.

[e] For women of childbearing potential. Serum or urine pregnancy test will be performed at Screening, at Baseline for each Treatment Period, and at the SFU Visit.

[f] Female study participants of nonchildbearing potential are to confirm their postmenopausal status.

[g] Vital signs will be evaluated predose and 3h (± 30 minutes) postdose for each morning dose. Blood pressure measurements will be performed in both supine and standing positions for orthostatic measurement at Screening (supine BP after the study participant has been lying down for 5 minutes and then standing BP after 1 minute and 3 minutes) and in a supine position for routine BP measurements at all assessments.

[h] Triplicate 12-lead ECG will be performed as immediate safety evaluations at Screening and Baseline. They will also be performed on each dosing day (approximately 3h [± 30 minutes] postdose), on each inpatient FU day, and at the SFU Visit. On D1 and D8 of each Treatment Period, the ECG recordings may be substituted with recordings from the Holter monitoring equipment, if they are immediately available for review. All 3 ECG recordings should be sufficiently separated so they have a different 'minute' on the timestamp, and all are to be performed within 4 minutes. All ECG recordings should be taken with the study participant resting in the supine position for ≥5 minutes before the recording.

[i] Holter monitoring will be performed for 24h at Screening. On D1and D8 of each Treatment Period, Holter monitoring will commence ≥1h prior to the morning dose of study medication, to enable extraction of the required predose ECGs. On D1 and D8, Holter monitoring is to continue for 24h following the morning dose (and until after collection of the following day's trough PK sample).

[j] A standardized light breakfast will be served; to be completed approximately 30 minutes prior to each morning dose, with the exception of D1 (morning) and D8 (morning) of each Treatment Period, when study participants will be dosed in fasted state (and will remain fasted for at least 2h postdose).

[k] On D1 and D8 of each Treatment Period, PK samples will be collected at 0.5h prior to the morning dose and at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h after dosing. An additional venous blood sample will be collected 18h after the D8 morning dose (D8 afternoon, 6h postdose sample).

[l] A venous blood sample will be collected at 0.5h prior to the morning dose (or at the time of the previous morning doses of study medication for days when dosing does not occur), for trough/ongoing PK concentration evaluation.

[m] Sample will be collected prior to the first dose of study medication on D1 of Treatment Period 1.

2 INTRODUCTION

2.1 Study rationale

Padsevonil is a novel chemical entity with selective affinity for both presynaptic SV2 isoforms and postsynaptic cBZR sites on the $GABA_A$ receptor that has shown broad-range efficacy in several preclinical models of epilepsy conducted by UCB.

The development program for PSL as an adjunctive treatment for focal-onset seizures in patients with epilepsy calls for the evaluation of its potential to affect cardiac repolarization, as indicated by prolongation of the HR-corrected QT interval on a standard 12-lead ECG.

Historically, such evaluations have been performed (in compliance with ICH Guideline E14, 2005) in large, rigorously controlled clinical studies, across a wide range of target drug exposure (C_{max}) levels that clearly bracket those to be anticipated in patients receiving the drug within the dosing regimen sought in the intended labelling.

However, in response to questions about the potential use of concentration-response analysis ('PK/PD modeling'), Revision 3 of the E14 Guidance (2017) provided clarification that such an analysis using adequate data from standard early phase clinical studies could provide the necessary evidence in place of a specific TQT study, if certain technical requirements were met.

UCB Pharma, having undertaken a detailed assessment of the data available from the early phase study program with PSL, believes those data to be sufficient to provide an acceptable evaluation across the C_{max} range associated with the anticipated labelled doses and lower, but not at the higher, supratherapeutic levels usually required by E14. The purpose of this study is, therefore, to gather data at the highest dose anticipated in labelling, 400mg bid (which is also the MTD for PSL), in comparison to both placebo and a 400mg moxifloxacin positive control (a drug known to have a prolongation effect on the QTc interval), to complete the dataset required.

This is a Phase 1, single-center, randomized, placebo-controlled, 3 treatment period crossover study to evaluate the effects of high-dose PSL on cardiac repolarization in healthy study participants. Moxifloxacin will be used as a positive pharmacologic control to allow demonstration of assay sensitivity.

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 anti-epileptic drugs (AEDs) modulate neuronal transmission by either blocking voltage-gated sodium channels or acting on inhibitory/excitatory receptors located at the postsynaptic level.

The $GABA_A$ receptor mediates the bulk of inhibitory neurotransmissions in the brain. Allosteric modulation of inhibitory $GABA_A$ receptors by the cBZR site offers robust protection against seizures (Riss et al, 2008). However, their clinical use as AEDs is limited due to an unfavorable side effect profile (eg, drowsiness, ataxia, amnesia, and paradoxical aggression), as well as the development of tolerance to anticonvulsant effects.

Compounds binding to SV2A proteins on synaptic vesicles are characterized by broad-spectrum efficacy against both generalized and partial seizures in preclinical models, and this protective

activity strongly correlates with their binding affinity (Kaminski et al, 2008). The function of SV2B and SV2C subtypes is not well established, but they share a high degree of sequence homology to SV2A and localization within synaptic vesicles (Wan et al, 2010; Janz and Südhof, 1999). Levetiracetam (LEV), exemplifying an 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 synergistic interaction observed between LEV and AEDs with GABAergic mechanisms of action (Kaminski et al, 2009). This synergistic interaction was particularly pronounced when combinations of LEV and benzodiazepines were tested and a significant increase in the anticonvulsant potency of these drugs was observed associated with a higher therapeutic index.

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-resistant epilepsy, suggesting superior efficacy against seizures resistant 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 produced seizure freedom only 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.

Padsevonil is cleared via metabolism involving the cytochrome P450 (CYP) pathway; the formation of the major metabolites, [redacted] is mainly mediated by CYP3A4, with potential involvement of CYP2C19. While [redacted] is an inactive metabolite, the [redacted] metabolite has been shown to have affinity for SV2A proteins (20-fold lower compared with PSL).

Because of its unique properties, PSL is currently being proposed as adjunctive therapy in the treatment of focal-onset seizures in adult patients with epilepsy.

2.3 Benefit/risk assessment

Overall, the clinical pharmacology and clinical studies in drug-resistant epilepsy demonstrated the 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) are consistent with adverse effects of other AEDs, including SV2A ligands. Events were transient, acute, and required admission to psychiatric care and medical treatment. The events in healthy study participants (n=2) occurred early after initiation or cessation of PSL, which was done without titration or tapering. The psychotic effect in an epilepsy study participant (Study EP0069) emerged after dramatic improvement in seizure control and electroencephalogram activity a few weeks after the start of PSL, suggesting a "forced normalization" (Clemens, 2005; Loganathan et al, 2015). Dose reduction of PSL and medical treatment resulted in complete resolution of psychosis within days, as the treatment with PSL continued. The occurrence of acute psychiatric effects in these 3 study participants administered PSL highlights the need to consider the possibility of significant psychiatric adverse effects and to maintain vigilance for such effects. The mitigation plan for acute psychiatric effects involves gradual titration and taper, which are known to improve tolerability of AEDs.

After the occurrence of several ECG findings (including different types of ectopy), both in healthy study participants and study participants with epilepsy, an independent expert cardiologist reviewed data from Phase 1 and Phase 2 studies and determined that none of these findings were assessed as being likely to be related to PSL. No clinically significant echocardiographic findings (only minor/trace or Grade 1 findings) were observed in Studies EP0069 and EP0073, and all echocardiograms were assessed as normal. There are currently no clinical data to suggest that PSL has an adverse effect on cardiovascular function other than a minimal lowering effect on BP. The degrees of reduction seen in both SBP and DBP are consistent with the $GABA_A$-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use. As a precaution 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 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.

The healthy study participants included in this study will receive no medical benefit from participation.

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.

3 OBJECTIVES AND ENDPOINTS

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

Table 3-1: Objectives and endpoints

Objectives	Endpoints
Primary	
The primary PD objective is: • To evaluate the effects on cardiac repolarization (QTc interval) of high-dose PSL in comparison to placebo in healthy study participants	The primary PD endpoint is: • Placebo-corrected change from Baseline in QTc, based on Fridericia's correction (QTcF) method (ΔΔQTcF) evaluated during the Target Dose Day of the PSL and placebo Treatment Periods, using time point analysis
Secondary	
The secondary PD objective is: • To evaluate other aspects of the effects on cardiac function of high-dose PSL in comparison with placebo and moxifloxacin	The secondary PD endpoints are: • Placebo-corrected change from Baseline in QTcF after a single dose of moxifloxacin • Placebo-corrected changes from Baseline for HR, PR interval, and QRS interval • Frequency of treatment-emergent changes for T-wave morphology and U-wave presence • Change from Baseline in QTcF (ΔQTcF) evaluated at drug-specific t_{max} (Δt_{max}) for PSL, [redacted] and possibly moxifloxacin
The secondary PK objective is: • To evaluate the plasma PK of PSL at steady state in healthy study participants	The secondary PK endpoints are: • $C_{max,ss}$, t_{max}, and AUC_{τ}, obtained from the plasma concentration-time profiles for PSL at steady state (on the Target Dose Day)
The secondary safety objective is: • To evaluate the safety and tolerability of PSL at the dosed level in healthy study participants	The secondary safety endpoints are: • Adverse events, SAEs, treatment-related AEs, and AEs leading to discontinuation of the study

Other	
The other PD objectives are: • To evaluate other aspects of the effects on cardiac function of high-dose PSL in comparison with placebo and moxifloxacin • To evaluate (using concentration-QT [C-QT] effect modeling) the relationship between QTc interval and the concentration of PSL and its metabolites	The other PD endpoints are: • Categorical outliers for HR, QTcF, PR interval, and QRS interval • Relationship between ΔQTcF (change from Baseline in QTcF) and the plasma concentrations of PSL, [redacted], and possibly moxifloxacin
The other PK objectives (depending on the outcome of PK and/or QT analyses) are: • To evaluate from plasma samples the PK of PSL and the major metabolites of PSL ([redacted]) • To evaluate from banked plasma samples the PK of moxifloxacin (if needed) in healthy study participants • To collect and store blood for possible ADME genotyping (if needed)	The other PK endpoints are: • For PSL: – Single dose: AUC_{0-12}, C_{max}, and t_{max} – Multiple dose: $CL_{ss/F}$ and C_{trough} • For PSL metabolites: – Single dose: AUC_{0-12}, C_{max}, t_{max}, and metabolic ratios for C_{max} and AUC_{0-12} – Multiple dose: AUC_{τ}, AUC_{0-t}, C_{trough}, $C_{max,ss}$, t_{max}, and metabolic ratios for $C_{max,ss}$ and AUC_{τ} • For moxifloxacin (if needed): – Single dose: AUC, AUC_{0-t}, $t_{½}$, C_{max}, and t_{max} • Possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL and metabolite PK analyses) (if needed)
The other safety objective is: • To evaluate safety and tolerability of PSL at the dosed level in healthy adult study participants	The other safety endpoints are: • Changes from Baseline in safety laboratory data (hematology, clinical chemistry, and urinalysis) • Changes from Baseline in vital signs (PR, respiratory rate, SBP, and DBP) • Changes from Baseline in 12-lead ECG assessment • Physical examination findings

ADME=absorption, distribution, metabolism, and excretion; AE=adverse event; C-QT=concentration-QT; ΔQTcF=time-matched, Baseline-subtracted QTcF; DBP=diastolic blood pressure; ECG=electrocardiogram; HR=heart rate; PD=pharmacodynamic; PK=pharmacokinetic; PR=pulse rate; PSL=padsevonil; QTc=QT interval corrected; QTcF=QT interval corrected for HR using the Fridericia method; SAE=serious adverse event; SBP=systolic blood pressure

4 STUDY DESIGN

4.1 Overall design

This is a Phase 1, single-center, randomized, placebo-controlled, crossover study to compare the PD effect on cardiac repolarization of high-dose PSL (400mg bid at steady state = MTD), with those of moxifloxacin (an open-label drug known to have a prolongation effect on the QTc interval) and placebo, in healthy study participants.

The target total duration of the study is 94 days for each study participant, including the Screening Period (up to 28 days), crossover dosing across 3 Treatment Periods (14 days per Treatment Period), 2 Washout Periods (7 days per Washout Period), and the SFU Visit (within 7 to 10 days after their discharge from the clinic). However, this may vary according to the scheduling of Treatment Periods.

The study schema is presented in Section 1.2 and the Schedule of activities is presented in Table 1-1.

4.1.1 Screening and Baseline Periods

The design uses a 3-Treatment Period crossover structure. Study participants who provide written informed consent will be screened within 28 days before the first Treatment Period. For further details regarding the assessments performed during the Screening and Baseline Periods, refer to the Schedule of activities (Table 1-1).

4.1.2 Treatment Periods 1, 2, and 3

During each Treatment Period, each study participant will check into the site the day prior to the relevant First Dosing Day. Throughout the relevant Dosing Days, continuous Holter monitoring will be undertaken to provide extracted ECG records at the relevant time points necessary to the evaluation of QT interval effects. During the hour prior to administration of the first dose of each Treatment Period, 3 triplicate ECGs extracted from the Holter record will serve to provide a time-averaged Baseline for that Treatment Period.

Subsequently, dosing with the allocated study medication will be initiated: for study participants in the PSL Treatment Period, the bid doses of PSL will be titrated up to reach steady state in time for the target dose on the 'Target Dose Day,' as shown in Figure 1-1.

The randomized dosing regimen will be as follows:

- In the PSL Treatment Period:
  - On Day 1, 100mg PSL will be administered bid, in the morning and the evening.
  - On Days 2 and 3, 200mg PSL will be administered bid, in the morning and the evening.
  - On Days 4 and 5, 300mg PSL will be administered bid, in the morning and the evening.
  - On Days 6 and 7, 400mg PSL will be administered bid, in the morning and evening.
  - On Day 8, the Target Dose Day, study participants will be fasted prior to the morning dose. Subsequently, 400mg PSL will be administered in the morning, and placebo will be administered in the evening.
  - On Day 9, 300mg PSL will be administered bid, in the morning and the evening.

  - On Day 10, 200mg PSL will be administered bid, in the morning and the evening.
  - On Day 11, 100mg PSL will be administered bid, in the morning and the evening.
- In the Placebo Treatment Period:
  - On Days 1 through 7, placebo to match the PSL Treatment Period doses will be administered bid, in the morning and the evening.
  - On Day 8, the Target Dose Day, study participants will be fasted prior to the morning dose. Subsequently, placebo to match 400mg PSL will be administered in the morning, and in the evening.
  - On Days 9 through 11, placebo to match the PSL Treatment Period doses will be administered bid, in the morning and the evening.
- In the MoxifloxacinTreatment Period:
  - On Days 1 through 7, placebo to match the PSL Treatment Period doses will be administered bid, in the morning and the evening.
  - On Day 8, the Target Dose Day, study participants will be fasted prior to the morning dose. Subsequently, 400mg moxifloxacin will be administered in the morning, and placebo will be administered in the evening.
  - On Days 9 through 11, placebo to match the PSL Treatment Period doses will be administered bid, in the morning and the evening.

On the morning of Day 1 of each Treatment Period, Holter ECG monitoring will be conducted at 0.75, 0.5, and 0.25 hours prior to the time of first dosing with study medication and until dosing, and a venous blood sample for PK analysis will also be drawn 0.5 hours prior to dosing. On the Target Dose Day of each Treatment Period (T1D8, T2D8, and T3D8), Holter ECG monitoring will be conducted from 1 hour prior to the morning dose of study medication and will continue for 24 hours afterwards. For a full description of Day 1 and Day 8 blood sampling time points, refer to the Schedule of activities (Table 1-1).

On the evening of the Target Dose Day for each Treatment Period, all study participants will receive placebo in order to protect the 18- and 24-hour PK/QT evaluations during the PSL Treatment Period.

On Days 3 through 7 and Days 10 through 21 of each Treatment Period, a venous blood sample will be taken prior to the morning dose / at the time of the previous morning doses of study medication, for trough / ongoing PK level evaluation. The blood samples will be used to measure plasma concentrations of PSL, [redacted], and [redacted], and possibly moxifloxacin, as well as for safety monitoring.

On Days 12, 13, and 14 of each Treatment Period, study participants will remain at the clinic for inpatient follow-up assessments.

The safety and tolerability of repeated doses of PSL will be monitored throughout the study by evaluation of AEs, psychiatric and mental status, C-SSRS, vital signs, 12-lead ECG parameters, physical and neurological examination findings, and clinical laboratory test results.

For further information, see the Schedule of activities (Table 1-1).

4.1.3 Washout Periods

Following completion of each Treatment Period, study participants will be discharged from the clinic, returning on the day prior to the First Dosing Day of the next Treatment Period for readmission. The interval between Treatment Periods (Washout Period) will be sufficient to ensure a minimum of 7 days' washout from the study medication administered during the previous Treatment Period.

4.1.4 Safety Follow-up Period

Following completion of the final Treatment Period, study participants will be discharged and return for an SFU Visit within 7 to 10 days after their discharge from the clinic.

4.2 Scientific rationale for study design

The development program for PSL as an adjunctive treatment for focal-onset seizures in patients with epilepsy calls for the evaluation of its potential to affect cardiac repolarization, as indicated by prolongation of the HR-corrected QT interval on a standard 12-lead ECG.

Historically, such evaluations have been performed (in compliance with ICH Guideline E14, 2005) in large, rigorously controlled clinical studies, across a wide range of target drug exposure (C_{max}) levels that clearly bracket those to be anticipated in patients receiving the drug within the dosing regimen sought in the intended labelling. Use of placebo and a positive control have also usually been mandatory in such TQT studies.

The FDA advocates use of moxifloxin as a positive control to confirm assay sensitivity in TQT studies. Because moxifloxin has a known QT-prolonging effect, the inclusion of moxifloxin in the treatment sequence will confirm that UP0050 is sensitive enough to demonstrate QT prolongation at thresholds of regulatory concern (FDA, Guidance for Industry, 06/2017).

The E14 Guidance recommends that – in the absence of any logistical or ethical reasons to do otherwise – the most appropriate population for TQT studies is a healthy population of male and female study participants.

In previous Phase 1 healthy volunteer studies, results from repeat bid PSL dosing suggest time-dependent inhibition of apparent clearance, with a mean exposure 1.7 times higher than anticipated PSL exposures and a longer time to achieve steady state. This implies that the single dose PK of PSL cannot be extrapolated linearly to the multiple dose scenario. Therefore, participants in this study will receive multiple doses of PSL, up-titrating from 100mg bid to 400mg bid, which has been demonstrated to increase tolerability. Steady state for both PSL and [redacted] is achieved following 2 to 3 days of PSL treatment. Therefore, the assessment day ('Target Dose Day') will be Day 8, by which time participants in the PSL treatment arm will be at steady state.

A double-blind technique will be used for PSL and its matching placebo, while a single-blind technique (with the PSL placebo) will be used for the moxifloxacin Treatment Period. Treatment sequence randomization will be undertaken using a double William's Latin square design in order to accommodate the single-blind nature of the moxifloxacin treatment period.

On the morning of Day 8, within each of the 3 treatment periods, participants will receive either 400mg PSL, a single 400mg dose of moxifloxacin, or placebo, according to their randomization

allocation. The treatment duration of the positive control, a single 400mg dose of moxifloxacin on Day 8, is deemed sufficiently long enough to exert the expected QT-related changes.

4.3 Justification for dose

Padsevonil was determined to have an MTD of 400mg bid with repeated dosing in healthy study participants for up to 12 days' duration (Study N01386). Most of the AEs affected the CNS and were consistent with the pharmacology of PSL; these events occurred in the absence of titration or tapering of PSL doses. The most commonly reported AE for study participants on PSL 400mg bid was somnolence (100%). Other AEs that occurred more frequently at the PSL 400mg bid dose included amnesia, ataxia, disturbance in attention, dizziness, and headache. The incidences of ataxia, diplopia, dizziness, headache, and somnolence increased with increasing dose of PSL (100mg bid to 400mg bid), while no clear dose dependence was observed for the majority of the other reported AEs (most of which were mild or moderate in intensity). However, 9 study participants treated with PSL experienced treatment-emergent adverse events (TEAEs) of severe intensity. Overall, the CNS AE profile showed some evidence of a dose relationship, was generally self-limiting, did not pose any significant risk to study participants, and was considered to be clinically manageable.

In studies conducted using titration and tapering of PSL doses, the 400mg dose of PSL is often associated with cognitive and motor impairment of mild to moderate intensity when administered as single and multiple doses to healthy study participants; therefore, PSL 400mg bid (the anticipated high therapeutic dose) has been selected as the high dose for this study.

Accordingly, because the primary objective of this study is to acquire data on the relationship between PSL C_{max} and QTc at the highest acceptable exposure level, the morning dose on the Target Dose Day (Day 8) of the PSL Treatment Period has been selected to be 400mg (at steady state), to provide an acceptable balance between the study objectives and the safety of the study participants.

Evaluation of any PD effect of PSL at the anticipated C_{max} levels with those of placebo and 400mg moxifloxacin – within the context of a rigorously performed 'Mini QT' study – is expected to provide the data required to satisfy the E14 requirement for the clinical evaluation of QT/QTc interval prolongation risk.

4.4 End of study definition

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

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

The maximum study duration per study participant is up to 94 days, including Screening (up to 28 days), 3 Treatment Periods (of up to 14 days each), 2 Washout Periods (of 7 days each), and the SFU Visit within 7 to 10 days after their discharge from the clinic.

5 STUDY POPULATION

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

5.1 Inclusion criteria

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

Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the ICF.

Type of participant and disease characteristics

2. Participant who is overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
   Note: Study participant has clinical laboratory test results within the local reference ranges or values that are considered as not clinically relevant by the Investigator and approved by the UCB Study Physician. Laboratory parameters outside the reference ranges can be retested and if the retest result is within the reference range or considered as clinically not relevant, the study participant will be allowed in the study.

Weight

3. Body weight of at least 50kg (males) or 45kg (females) and body mass index (BMI) within the range 18 to 30kg/m^2 (inclusive).

Sex

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

Informed consent

5. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
6. Participant must be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator, and is capable of communicating satisfactorily with the Investigator.

5.2 Exclusion criteria

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

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study, such as a history of schizophrenia or other psychotic disorder, bipolar disorder, or severe unipolar depression. The presence of potential psychiatric exclusion criteria will be determined based on the psychiatric history collected at the Screening Visit.
2. 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. Participant has a history of chronic alcohol or drug abuse within the previous 6 months.
4. Participant has a positive prestudy drug/alcohol screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines).

   Note: A 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. Participant has a known hypersensitivity to any components of the study medication or comparative drugs as stated in this protocol or history of tendon pathology secondary to use of quinolone antibiotics.
6. Participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
7. Participant has a present condition of respiratory or cardiovascular disorders, eg, cardiac insufficiency, coronary heart disease, hypertension, arrhythmia, tachyarrhythmia, or myocardial infarction.
8. Abnormal BP. Note: This includes both the routine and orthostatic hypotension BP assessments. For routine BP, participant must have BP and PR within normal range in the supine position after 5 minutes of rest (SBP: 90mmHg to 140mmHg; DBP: 40mmHg to 90mmHg; PR: 40bpm to 100bpm). Any values marginally (ie, no more than 5mmHg) outside the normal range but considered not clinically significant by the Investigator would be allowed. In case of an out of range result, 1 repeat will be allowed. If the readings are out of range again, the study participant will not be included.
9. 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

10. Participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has had suicidal ideation in the past 6 months as indicated by

a positive response ("Yes") to either Question 4 or Question 5 of the "Screening/Baseline" version of the C-SSRS at Screening.

Prior/concomitant therapy

11. Past or intended use of over-the-counter (OTC) 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.
12. Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin, etc) within 2 months prior to the first dose of study medication. In case of uncertainty, the UCB Study Physician should be consulted.

Prior/concurrent clinical study experience

13. Participant has previously received PSL in this or any other study.
14. Participant has participated in another study of a study medication (and/or an investigational device) within the previous 30 days or 5 half-lives (whichever is longer) or is currently participating in another study of a study medication (and/or an investigational device).

Diagnostic assessments

15. Participant has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0x ULN.

    Participant has bilirubin >1.0xULN (isolated bilirubin <1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
17. Participant has any clinically relevant ECG finding at the Screening Visit or at Baseline. 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 participant with any of the following findings will be excluded:
    a. QTcF ≥450ms (on mean of triplicate ECG recordings);
    b. Other conduction abnormalities (defined as PR interval >220ms);
    c. QRS interval >109ms;
    d. Any rhythm other than sinus rhythm;
    e. Any history of Wolff-Parkinson-White Syndrome, Brugada Syndrome, unexplained syncope, or ventricular tachycardia;
    f. Family history of QTc prolongation or of unexplainable sudden death at <50 years of age

    In case of an out of range result, 1 repeat will be allowed. If out of range again, the participant cannot be included.

    NOTE A: The QTc is the QT interval corrected for HR according to Bazett's formula (QTcB), 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 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 participant and then the lowest QTc value used to include or discontinue the participant.

18. Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to dosing.
19. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention. NOTE: 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.
20. Positive human immunodeficiency virus (HIV) antibody test.

Other exclusions

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

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Refrain from consumption of grapefruit, starfruit, and pawpaw as beverage, fruit or supplements) from 3 days before the start of study medication until after the final dose.
- On Day 1 and Day 8, study participants will be in the fasted state prior to the morning dosing and until approximately 2 hours postdose, and the standard evening meal will be completed approximately 30 minutes prior to dosing.

- On the dosing days (other than Day 1 and Day 8), participants will consume a light meal approximately 30 minutes prior to each morning dose and will consume a standard meal approximately 30 minutes prior to each evening dose. Other meals during the day will be allowed, provided consistent timing and similar meal content are maintained during Treatment Periods. Timing may vary depending on assessements collected in close proximity to meal administration; however, every effort will be made to ensure a consistent meal schedule is adhered to during Treament Periods. On nondosing days, morning and evening meals will be completed approximately 30 minutes prior to dosing, and other meals (and content) may be consumed at the site's discretion.

  Minor departures from the above 30 minute interval are permitted, but the following situations will be handled as protocol deviations:

  – No meal is consumed
  – Study medication is taken prior to commencing the meal
  – Study medication is taken >1 hour following completion of the meal

- Padsevonil will be administered orally with 240mL (8oz) water. Between 1 hour predose and 2 hours postdose, the total intake of beverages should be limited to 100mL. Water will be available ad libitum except for between 1 hour before and 2 hours after dosing.

5.3.2 Caffeine, alcohol, and tobacco

- During each dosing session, 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 and/or PD sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3 Activity

- From Screening through the SFU Visit, participants will abstain from strenuous exercise. Participants may participate in light recreational activities during studies (eg, watching television, reading).

5.4 Screen failures

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

5.4.1 Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Study participants may be rescreened under conditions such as the following:

- Study participant ingests grapefruit (as beverage, fruit, or supplements) within 72 hours before each administration of study medication.
- If a study participant does not meet the exclusion criteria at the Screening Visit (Days -21 to -2) or at the Baseline Visits (Day -1 of each Treatment Period) 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 participant 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 or moderate illness, and if all other screening criteria are met.
- Rescreened participants should be assigned the same participant number as for the initial screening.
- Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

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. Further guidance and information regarding study treatments are provided in the UP0050 Investigational Medicinal Product (IMP) Handling Manual.

6.1 Treatments administered

A summary of the treatments administered is provided in Table 6-1. Further guidance or information is provided in the IMP Handling Manual.

Table 6-1: Treatments administered

Study Treatment Name:	PSL	Moxifloxacin	Placebo
Dosage formulation:	Tablet	Tablet	Tablet
Dosage levels:	100mg, 200mg, 300mg, and 400mg bid	400mg	To match PSL 100mg, 200mg, 300mg, and 400mg bid
Route of administration:	Oral	Oral	Oral
Dosing instructions:	Dosing instructions are provided in the UP0050 IMP Handling Manual (IP Instruction for Handling).		
Packaging and labeling:	Padsevonil tablets are manufactured, packaged, and labeled according to GMP guidelines and applicable laws or regulations.	Moxifloxacin tablets are manufactured, packaged, and labeled according to GMP guidelines and applicable laws or regulations.	Placebo to match PSL tablets are manufactured, packaged, and labeled according to GMP guidelines and applicable laws or regulations.
Manufacturer:	UCB	Accord Healthcare Ltd.	UCB

bid=twice daily dosing; GMP=Good Manufacturing Practice; IMP=investigational medicinal product; IP=investigational product; PSL=padsevonil

6.2 Preparation, handling, storage, and accountability requirements

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

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

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

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the UP0050 IMP Handling Manual.

Further guidance and information for the final disposition of unused study medication are provided in the UP0050 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 (SOPs) or returned to UCB (or designee). Study medications 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

A contract research organization (CRO; ie, ICON) randomization biostatistician will create the program to generate the randomization code and code break envelopes. The randomization biostatistician will be independent of the study. A dummy randomization schedule will be prepared by the randomization biostatistician (ICON) and reviewed by the Clinical Study Biostatistician in order to ensure that the code meets the study requirements.

After finalization of the dummy code, the randomization program will be run with a different seed number to create the final randomization list; the final list will be generated in a secure environment and will be reviewed by a quality control randomization biostatistician, also independent of the study. This randomization list will be retained by the unblinded randomization biostatistician and study pharmacist until the end of the study (ie, until after database lock). The treatment assignment will be random.

Copies of the randomization lists will be sent before the start of the study in a secure fashion directly from the contracted CRO to:

- Sponsor Patient Safety (PS) staff for SAE reporting (sealed envelope)
- Bioanalytical staff (to identify samples to be measured)
- Unblinded member of pharmacy involved in study medication preparation and dispensing
- Independent Biostatistician/Early Statistical Programmer

In addition, staff involved in the analysis of unblinded PK data, such as a representative from the UCB Clinical Pharmacology/ Modeling and Simulation team and an unblinded monitor, will have access to the unblinded data during the study.

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

Once the Investigator determines that the study participant is eligible for the study, and before study medication administration, a central person in charge of issuing the randomization numbers will manually allocate a randomization number to the study participant (one for each study part) and communicate the randomization assignment to the unblinded site pharmacist. Each specific randomization number will be linked to the treatment allocation on the randomization schedule, which will be dispensed by the unblinded site pharmacist. The randomization numbers will also be recorded in the eCRF.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All participant treatment details (treatments, Treatment Period, and treatment sequences) will be allocated and maintained through the use of randomization lists and code break envelopes (or equivalent).

6.3.1.1.1 PSL and matching placebo

A site pharmacist who is not a member of the study team (has no responsibilities for study participant assessments) will prepare PSL or PSL placebo treatment from bulk supplies in accordance with the randomization schedule supplied by the ICON unblinded randomization statistician.

6.3.1.2 Breaking the treatment blind in an emergency situation

A code break envelope (or equivalent) containing the randomization code will be printed for each participant in a double-blind study and must not be broken, except for emergency situations. The Clinical Project Manager (CPM) must be informed immediately when a code is broken, but should remain blinded to specific treatment information. Any unblinding of the study medication

performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

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 medications/treatments

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- Paracetamol/acetaminophen for the treatment of mild symptoms (eg, headache or other pain), given at most every 6 hours to 8 hours, not exceeding 2g per day, and with a total of no more than 5g over 7 days.
- Ibuprofen, not exceeding 1.2g per day.
- Inhaled corticosteroids for seasonal rhinitis and topical corticosteroids for controlled dermatological conditions.
- Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or intrauterine devices/intrauterine systems delivering progesterone (for female study participants).

6.5.2 Prohibited concomitant treatments (medications and therapies)

With the exception of permitted concomitant treatments listed in Section 6.5.1, the following concomitant medications are prohibited during the study:

- All prescription or nonprescription medicines, are prohibited within 2 weeks or 5 half-lives (whichever is longer) before administration of study medication and during the clinical part of the study, unless required to treat an AE. This includes all OTC remedies, vitamins, and herbal and dietary supplements (including St John's Wort).
  - Hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin, etc.) should not be used within 2 months prior to dosing. In case of uncertainty, the UCB Study Physician should be consulted.
- Drugs of unknown half-lives are prohibited within 2 weeks before administration of study medication and during the clinical part of the study, unless required to treat an AE.

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

6.5.3 Rescue medication

Not applicable.

6.6 Dose modification

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

6.7 Treatment after the end of the study

There are no plans for participant 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.

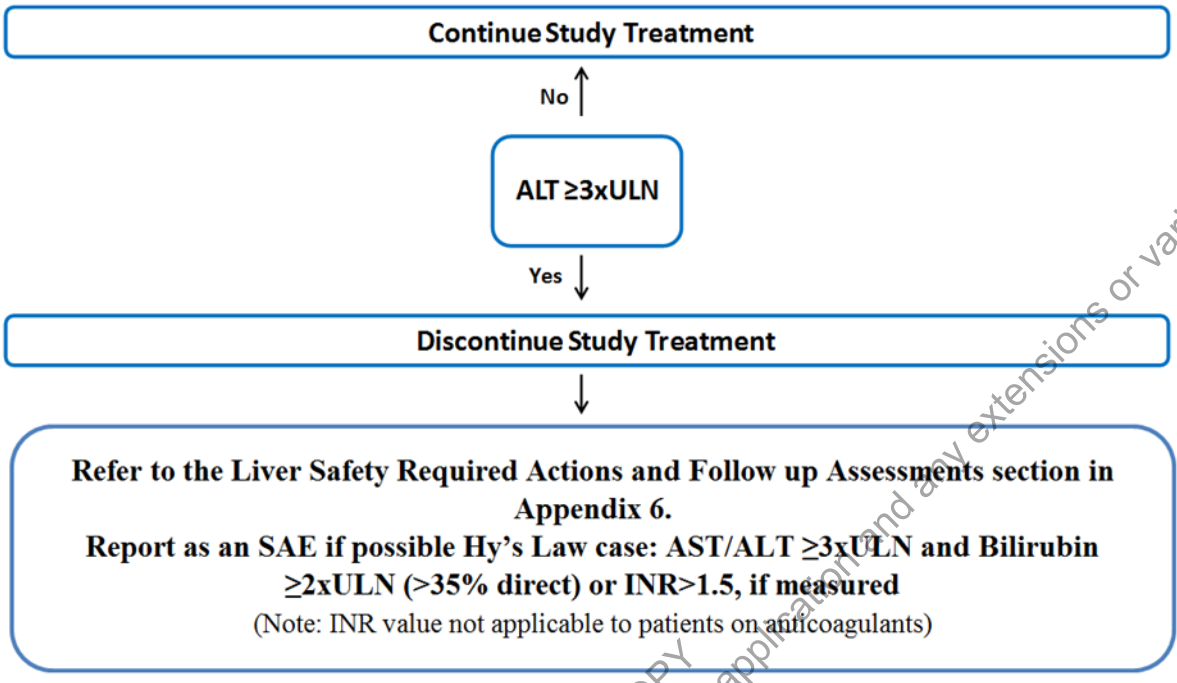
In all cases, the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB Study Physician. If a participant discontinues study medication, no restart will be allowed.

7.1.1 Liver chemistry stopping criteria

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

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

Figure 7-1: Liver chemistry stopping algorithm



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

Specific assessments and follow up actions for potential drug-induced liver injury are provided in Appendix 6 (Section 10.6). Discontinuation of study medication for abnormal liver function should be considered by the Investigator when a study participant meets 1 of the conditions outlined in the algorithm or if the Investigator believes that it is in best interest of the study participant.

7.1.2 QTc stopping criteria

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study.

- QTc >500ms
- Change from Baseline: QTc >60ms

See the Schedule of activities (Table 1-1) for data to be collected at the time of treatment discontinuation and follow up and for any further evaluations that need to be completed.

7.1.3 Study hold/stopping rules

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

- A serious adverse reaction (SAR) (ie, an SAE considered at least possibly related to the study medication) in 1 study participant;
- A severe nonserious adverse reaction (ie, severe nonserious AEs considered at least possibly related to the study medication administration) in 2 study participants in the same cohort, independent of within or not within the same SOC.

If either stopping criterion is met, the study will be put on temporary halt. In the event that either or both of the stopping criteria are met, a safety review will be immediately initiated. The safety review will be conducted by an internal, study-specific Safety Monitoring Committee comprised of the Investigator and appropriate members of the UCB Study Team (such as Study Physician, Safety Physician, Clinical Project Manager, Clinical Pharmacologist), as quickly as possible, to review the available data and determine whether it is appropriate to continue dosing at the next scheduled dosing point. This will take the form of a risk/benefit evaluation from the perspective of the individual study participants. In making this evaluation, account will be taken of the potential risks of sudden discontinuation of study medication, particularly in participants who may be taking higher dose levels, and whether or not a tapering period, and its duration/speed, should be undertaken.

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

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

7.1.4 Temporary discontinuation

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

7.1.5 Rechallenge

No rechallenge will be permitted.

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 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations to be completed.

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

1. Study participant develops a clinically relevant medical condition (physical or psychiatric) that, 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. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Study participant takes prohibited concomitant medications as defined in this protocol.
4. Study participant withdraws his/her consent.
5. The Sponsor or a regulatory agency requests withdrawal of the study participant.
6. Study participant has changes in the ECG that are regarded as clinically significant and/or that worsens over time. An ECG shows an absolute value for QTcB or QTcF ≥500ms or ≥60ms above Baseline.
7. Study participant develops second- or third-degree atrioventricular block or another clinically relevant change in ECG as determined by the Investigator.
8. Participant has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The study participant should be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgment of the benefit/risk ratio of continuing the study participant in the study on PSL.
   - Participant has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The study participant should be referred immediately to a mental healthcare professional and must be withdrawn from the study.
9. 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 particpants should follow the 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.

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

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

Protocol waivers or exemptions are not allowed.

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

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all

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 1-1).

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 Efficacy assessments

Not applicable.

8.2 Pharmacodynamics assessments

8.2.1 ECG/continuous Holter monitoring

Pharmacodynamics will be assessed via ECG (placebo-corrected ΔQTcF). The 12-lead Holter and ECG equipment will be supplied and supported by ERT. All ECG data will be collected using a Global Instrumentation (Manlius, NY, US) M12R ECG continuous 12-lead digital recorder. The continuous 12-lead digital ECG data will be stored onto secure digital memory cards. Electrocardiograms to be used in the analyses will be selected by predetermined time points as defined in the Schedule of activities (Table 1-1) and will be read centrally by ERT. On Day 1 and Day 8 of each Treatment Period, continuous Holter monitoring will be recorded from ≥1 hour predose until after collection of the PK sample 24 hours postdose (trough sample of the following day) using a M12R continuous 12-lead Holter/ECG device. Expert Precision QT will enable extraction of up to 10 replicate ECGs per time point. Each study participant should be assigned 1 M12R continuous 12-lead Holter/ECG device throughout the study. Study participants will remain resting in supine position and in a controlled, calm environment for 15 minutes prior to PK sampling time. Extracted ECG records at the relevant time points will be used for the evaluation of QT interval effects. During the hour prior to administration of the first dose of each Treatment Period, up to 10 replicate ECGs extracted from the Holter record (at -0.75, -0.5, and -0.25 hours) will serve to provide a predose time-averaged Baseline for that Treatment Period (seeTable 1-1).

The data will be analyzed using a standard ECG extraction protocol by ERT. Further detail will be provided in the SAP.

8.3 Pharmacokinetics assessments

Whole blood will be collected for measurement of plasma concentrations of PSL, its metabolites, and moxifloxacin, as specified in the Schedule of activities (Table 1-1). 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, its metabolites, and moxifloxacin plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to the investigative site or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

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

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

Table 8-1: Irrelevant time deviations for PK sampling

Pharmacokinetic blood sampling times (hours)	Deviation from scheduled time considered irrelevant (minutes)
0 (predose)	60 (prior to dosing)
0.25 to 1.5	2
2 to 8	5
12	15
24 to 48	60

PK=pharmacokinetic

8.4 Safety assessments

The safety and tolerability of single and multiple doses of PSL will be monitored by evaluation of AEs, clinical laboratory test results, vital signs (PR, RR, 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 1-1).

8.4.1 Physical examination

Physical examinations will be performed at Screening and at the time points specified in the Schedule of activities (Table 1-1).

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

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

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

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

8.4.2 Vital signs

Body temperature, PR, respiratory rate, and BP will be assessed as outlined in the Schedule of activities (Table 1-1).

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

Blood pressure measurements will be performed in both supine and standing positions for orthostatic measurement at Screening (supine BP after the study participant has been lying down for 5 minutes, then standing BP after 1 minute and 3 minutes), and in a supine position for routine BP measurements at all other 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 participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 BP measurement. Vital signs will be evaluated predose and 3 hours postdose for each morning dose.

8.4.3 Safety 12-lead ECGs

Triplicate 12-lead ECGs will be obtained as outlined in the Schedule of activities (Table 1-1) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

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

On Day 1 and Day 8 of each Treatment Period, when Holter monitoring is in place, the ECG recordings may be substituted with hardcopy ECGs extracted from the Holter monitoring equipment, if they can be made immediately available for safety review.

At each time point at which triplicate ECG are required for safety, all 3 recordings should be sufficiently separated so that they have a different 'minute' on the timestamp, and all are to be performed within 4 minutes.

Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.4.4 Clinical safety laboratory assessments

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

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

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

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the 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 1-1).

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

8.4.5 Suicidal risk monitoring

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

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study.

All study participants will complete the "Screening" version of the C-SSRS at the Screening Visit (Days -28 to -2) (assessing the past 6 months) or Baseline Visit (Day -1) for each Treatment Period, followed by the "Since Last Visit" version at the Day 14 Visit and the SFU Visit (Days 21 to 24), as indicated on the Schedule of activities (Table 1-1).

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

8.4.6 Psychiatric and mental status

The psychiatric and mental status of participating study participants will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. All study participants will undergo psychiatric/mental status evaluation at Screening and at the time points indicated on the Schedule of activities (Table 1-1).

The parameters that will be evaluated are orientation, attention, memory, mood, calculus, behavior, and thinking or feeling. These parameters will be assessed as normal or abnormal and

then determined whether clinically significant. If present and abnormal, psychiatric symptoms, mental impairment, and behavioral problems will be assessed as to whether they are clinically significant.

8.5 Adverse events

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

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the study participant to discontinue UP0050 or PSL (see Section 7).

8.5.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF and at the time points specified in the Schedule of activities (Table 1-1).

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

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

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

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

8.5.2 Method of detecting AEs and SAEs

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

8.5.3 Follow-up of AEs and SAEs

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

8.5.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to UCB of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of 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, 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 according to local regulatory requirements.

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

8.5.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants, will be collected after the start of study medication and until 30 days after the birth for any significant medical issues, but preferably up to 12 months after the birth. If the study participant is lost to follow up and/or refuses to give information, written documentation of attempts to contact the study participant needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

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

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

- The participant should return for an End of Study (EOS)/End of Treatment (EOT) Visit.
- The participant should immediately stop the intake of the study medication or be down-titrated as instructed at the EOS/EOT Visit.

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

8.5.6 AESI

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 UCB 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 participant.

8.6 Safety signal detection

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

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

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

8.7 Treatment of overdose

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

UCB does not recommend any specific treatment for an overdose.

In the event of an overdose, the Investigator should:

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

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

8.8 Genetics

Blood samples will be collected prior to the first dose of study medication on Day 1 of Treatment Period 1 and stored for possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL and metabolite PK analyses, if required).

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Medical resource utilization and health economics

Medical resource utilization and health economics are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set (ES): All study participants who have signed the ICF.
- Randomized Set (RS): All enrolled study participants who are randomized will be included in the RS.
- Safety Set (SS): All enrolled study participants who receive at least 1 dose of study medication.
- Pharmacokinetic Per-Protocol Set (PK-PPS): All enrolled study participants who receive at least 1 dose of study medication and who have no important protocol deviations affecting the PK and for whom at least 1 measurable concentration is available.

For definitions of the Pharmacodynamic Per-Protocol Set (PD-PPS) and other relevant PD analysis sets, refer to the SAP.

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 (SD), minimum, and maximum (geometric mean and geometric coefficient of variation [CV] for plasma concentrations and PK parameters). Categorical endpoints will be summarized using number of study participants, frequency, and percentages. Missing data will not be imputed.

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

9.3 Planned efficacy/outcome analyses

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

9.4 Planned PD analyses

9.4.1 Analysis of the primary ECG endpoint

During the hour prior to administration of the first dose of each Treatment Period, up to 10 replicate ECGs extracted from the Holter record (at -0.75, -0.5, and -0.25 hours) will serve to provide a predose time-averaged Baseline for that Treatment Period and use to compute change from Baseline QTcF (ΔQTcF).

The primary objective of evaluating the effects on QTc interval of high-dose PSL in comparison to placebo will be analyzed as follows:

- The primary analysis will be based on a by-time point analysis to evaluate the effect of PSL on the ΔΔQTcF at each postdose time point using the Intersection Union Test (IUT). Moxifloxacin will be used for confirmation of assay sensitivity.

Further detail on the primary endpoint analysis will be provided in the SAP.

9.4.2 Analysis of the secondary ECG endpoints

The secondary effects on cardiac repolarization (QTc interval) of high-dose PSL in comparison with placebo and moxifloxacin will be analyzed as follows:

- The effect of PSL on placebo-corrected change from Baseline in HR, PR, and QRS (ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated using the IUT.
- Assay sensitivity will also be evaluated using by-time point analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis.
- An analysis of categorical outliers will be performed for changes in HR, QTcF, PR, QRS, T-wave morphology and U-wave presence.
- The Δt_{max} will be evaluated using an analysis of variance (ANOVA) mixed-effect model by study drug (PSL 400mg bid, and moxifloxacin 400mg), with the treatment (active treatment and placebo) as fixed effects. A 95% one-sided confidence interval (CI) (equivalent to 90% two-sided CI) of the mean difference between each active treatment and placebo will be derived from ANOVA.

Further detail on the secondary endpoint analyses will be provided in the SAP.

9.4.3 Analysis of the other PD endpoints

Results of the other PD endpoints and analyses will be reported in either the Clinical Study Report or an overarching Cardiac Safety Report.

- The relationship between plasma concentrations of PSL and its major metabolites [redacted] and ΔQTcF will be evaluated using a linear mixed-effects modeling approach (Garnett et al, 2018).

9.5 Planned PK analyses

The planned PK analyses will be estimated using noncompartmental analysis (NCA) with Pharsight Phoenix® WinNonlin® v6.3 (or higher) software.

The planned secondary PK endpoints of PSL include the parameters $C_{max,ss}$, t_{max}, and AUC_{τ} at steady state (Target Dose Day [Day 8]).

The planned other PK endpoints of PSL include the parameters AUC_{0-12}, C_{max}, and t_{max} (single dose), and $CL_{ss/F}$ and C_{trough} (multiple dose).

The planned other PK endpoints of the major metabolites of PSL ([redacted]) include the parameters AUC_{0-12}, C_{max}, t_{max}, and metabolic ratios for C_{max} and AUC_{0-12} (single dose) and AUC_t, AUC_{0-t}, $CL_{ss/F}$, C_{trough}, $C_{max,ss}$, t_{max} and metabolic ratios for $C_{max,ss}$ and AUC_{τ} (multiple dose).

If required, the planned other PK endpoints of moxifloxacin include the parameters AUC, AUC_{0-t}, $t_{½}$, $C_{max,}$ and t_{max} (single dose).

The individual plasma concentrations and PK parameters of PSL, [redacted] and possibly moxifloxacin will be summarized by day (Day 1 or Day 8) using descriptive statistics (number of observations, geometric mean, lower and upper 95% CI, geometric CV, arithmetic mean, SD and CV, median, and minimum and maximum value) and graphical displays.

9.6 Planned safety analyses

All safety analyses will be performed using the SS. All safety variables will be listed and summarized by each study part and treatment.

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 medications. All AE data will be listed by study participant number, visit, treatment, and time. The listings will include the following data pertaining to the AEs: start and end dates with relative days to study medication administration, duration, intensity, seriousness, relationship to study medication, action taken, and final outcome.

The occurrence and incidence of TEAEs will be summarized by study part according to the intake of study medication (pretreatment or treatment-emergent) and by intensity or relationship to PSL.

Safety laboratory measurements, vital signs, and 12-lead/Holter ECG parameters will be tabulated by Treatment Period using descriptive statistics. Laboratory values outside the reference range will be flagged in the listings. Any PDILI events will be listed.

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

Physical and neurological examination abnormalities will be listed.

9.7 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 (or primary PD outcome) for an individual study participant. Study participants will be excluded from the PK-PPS (or PD-PPS) only when there is documented evidence that they received no treatment. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the relevant protocol deviation specification document, which is part of the study Data Cleaning Plan. To the extent feasible, rules for identifying protocol

deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all study participants.

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

9.8 Handling of dropouts or missing data

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

9.9 Planned interim analysis and data monitoring

No formal interim analyses are planned.

9.10 Determination of sample size

The sample size for this study is based on the most stringent of the requirements for the test compound (PSL) and for the positive control (moxifloxacin).

A sample size of up to 54 study participants was chosen to obtain 49 evaluable study participants who will complete the study. Assuming a 1-sided 5% significance level and a within-study participant SD of 8ms for ΔQTcF for all treatment groups and a true mean difference of 3ms in ΔQTcF between PSL and placebo, based on the calculation of the sample size for a TQT study (Zhang and Machado, 2008), a sample size of 49 evaluable study participants will provide a power of 96% to demonstrate that the upper limit of all the 2-sided 90% CIs on ΔΔQTcF will fall below 10ms for up to 11 postdose time points.

Sample size calculation for assay sensitivity: Based on the calculation of the sample size for a TQT study (Zhang and Machado, 2008), as the test will be performed at 3 prespecified time points separately, a one-sided 5% significance level (with adjusted one-sided significance levels of 5%, 2.5%, and 1.67%) will be used in addition to a within-study participant SD of 8ms for ΔQTcF and a true effect of moxifloxacin of 10ms. A sample size of 49 evaluable study participants will provide a power of 99% to demonstrate assay sensitivity of excluding a mean difference of 5ms in ΔQTcF between moxifloxacin and placebo groups, ie, the lower limit of the 2-sided 90% CI of ΔΔQTcF will exceed 5msec at least one of the 3 prespecified time points.

To achieve a balanced design, and to allow for a few dropouts, it is planned to recruit up to 54 study participants.

Dropouts may be replaced at the discretion of the principal Investigator and Sponsor, depending on the circumstances.

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

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

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO 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 participant in both oral and written form by the Investigator (or designee). Each study participant will have the opportunity to discuss the study and its alternatives with the Investigator.

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

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

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

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 participant number assigned at Screening.

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

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 IEC members, and by inspectors from regulatory authorities.

10.1.5 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 eCRF.

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

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

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

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

All essential documents are to be retained by the Investigator until ≥2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or ≥2 years have elapsed since the formal discontinuation of clinical development of the study medication. 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.

10.1.5.1 Case Report Form completion

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

Any change or correction to the eCRF after saving must be accompanied by a reason for the change. Use of correction fluid is not permitted.

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.5.2 Apps

Not applicable.

10.1.6 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, or optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include clinic records, charts, laboratory results, printouts, pharmacy records, ECG or other printouts, or completed scales, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

10.1.7 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 IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study medication development.
  - 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 Table 10-1 below will be performed by a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10-1: Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
Hematology[a]	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocyte count	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a b]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal) • Urine hCG pregnancy test (as needed for WOCBP) at each Baseline and the SFU Visit[c]			
Other Screening Tests	• FSH and estradiol (as needed in women of nonchildbearing potential only) • Alcohol breath test and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum hCG pregnancy test (as needed for WOCBP)[c] • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) The results of each test must be entered into the eCRF.			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; UL=upper limit; ULN=upper limit of normal; WBC=white blood cell; WOCBP=woman of childbearing potential

[a] Hematology, clinical chemistry, and urinalysis assessments will be performed nonfasting.
[b] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6. All events of ALT ≥3XUL and bilirubin ≥2XULN (>35% direct bilirubin) or ALT ≥3XULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IEC. Serum pregnancy test will be performed at Screening.

The Investigator must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to the investigative site or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse Events – Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

10.3.2 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Important medical events:

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

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 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 participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AESIs.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any postmortem 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.

10.3.4 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

Definitions

Woman of childbearing potential (WOCBP)

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

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

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

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

Contraception guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition male participants must refrain from donating sperm for the duration of the study and for at least 90 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 at least 90 days after the final dose of study medication.

Pregnancy testing

- A WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at the Screening Visit (Days -28 to -2).
- Urine or serum pregnancy testing should be performed at Screening, each Baseline Visit (Day -1 of each Treatment Period) and at the SFU Visit, after the last dose of study medication, and as required locally. The result must be negative prior to dosing the study participant.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Should a serum pregnancy test not be available, a urine pregnancy test with a sensitivity of 10mIU/mL will be performed at the Screening Visit (Days -28 to -2), each Baseline Visit (Day -1 of each Treatment Period), and at the SFU Visit. The result must be negative prior to dosing the study participant.

Collection of pregnancy information

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-2.

Table 10-2: 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
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

IUD=intrauterine device; IUS=intrauterine system; WOCBP=woman of childbearing potential

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for study participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, a suitable additional barrier method of contraception (ie, condom) should be utilized during the treatment period and for at least 90 days, corresponding to time needed to eliminate study medication plus 30 days for study medications with genotoxic potential after the last dose of study medication.

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.

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 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 participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 30 days (or up to 12 months) after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.5.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female study participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – Suggested Actions and Follow-up Assessments

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

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

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

A specific monitoring plan must be agreed between the UCB Study Physician and the Investigator for study participants who have ALT >3 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 (see Table 10-3).

Table 10-3: Phase I liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria	
ALT-absolute	ALT≥3xULN If ALT ≥3xULN **AND** bilirubin ≥2xULN (>35% direct bilirubin) OR INR >1.5, report as an SAE[a,b] See additional actions and follow-up assessments listed below
Required actions and follow-up assessments	
Actions	**Follow-up assessments**
• Report the event to UCB **within 24 hours** • Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE[a] • Perform liver chemistry follow-up assessments • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**) • Consider the need for a toxicology screening **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform	• Viral hepatitis serology[c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis as soon as possible after the most recent dose • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia

liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline • A specialist or hepatology consultation is recommended **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other OTC medications) on the concomitant medications eCRF • Record alcohol use on the liver event alcohol intake eCRF **<u>If</u> ALT ≥3xULN AND bilirubin ≥2xULN <u>or INR</u> >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al, 2009].) **NOTE: Not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HPLC=high performance liquid chromatography; Ig=immunoglobulin; INR=international normalized ratio; LDH=lactate dehydrogenase; OTC=over-the-counter; RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal

[a] 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.

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

[c] Hepatitis A 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	anti-epileptic drug
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
bid	twice daily dosing
cBZR	postsynaptic central benzodiazepine receptor
CI	confidence interval
CNS	central nervous system
CPM	Clinical Project Manager
C-QT	concentration-QT
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
D	Day
DBP	diastolic blood pressure
Δ	change from Baseline
ΔΔQTcF	placebo-corrected change from Baseline
ECG	electrocardiogram
eCRF	electronic Case Report form
EOS	End of Study
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
$GABA_A$	gamma-aminobutyric acid-A
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IUT	Intersection Union Test
LEV	levetiracetam
MTD	maximum tolerated dose
NCA	noncompartmental analysis
OTC	over-the-counter
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per-Protocol Set
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PR	pulse rate
PS	Patient Safety
PSL	padsevonil
QTc	QT interval corrected
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate using the Fridericia method
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-up
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SV2	presynaptic vesicle protein 2
TEAE	treatment-emergent adverse event
TQT	Thorough QT
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol Amendment History

Amendment 1 (10 Oct 2019)

Overall Rationale for the Amendment

The protocol has been amended to comply with the requirement of the Medicines and Healthcare products Regulatory Agency (MHRA). Changes were made in the exclusion criteria to set the upper limit of acceptable range of total bilirubin test results and to clarify language regarding liver function tests (absolute rule for liver function test parameters) for alignment with regulatory requests in another padsevonil (PSL) protocol. Changes were made in Section 7.1.3 (Criteria for study hold due to adverse events) to comply with an MHRA requirement to align with European Medicines Agency Guidance on risk mitigation in first-in-human and early clinical trials. In addition, further changes have been made to correct various other typographical errors and to add clarifying language.

Section # and Name	Description of Change	Brief Rationale
Section 3 Table 3-1	Language regarding a secondary endpoint was removed.	This is a correction to align information in the objective and endpoints section of the summary along with the information in the Schedule of activities (Table 1-1).
Section 5.2-Exclusion Criteria	Changed exclusion criterion #15 to include that isolated bilirubin must be <1.5x upper limit of normal (ULN) instead of >1xULN. Exclusion criterion #15 had the note removed regarding liver function test values above the ULN and repeat tests that could be performed in such situations. Language regarding retesting of participants with out-of-range laboratory values remains elsewhere in the protocol including Section 5.4.1 (Rescreening).	Update exclusion criteria
Section 5.2-Exclusion Criteria	The exception of asymptomatic gallstones was removed from exclusion criterion #16.	Update exclusion criteria
Section 6.1 Table 6-1 Treatments administered	The manufacturer of moxifloxacin has been updated from Bayer to Accord Healthcare, Ltd.	Correction
Section 7.1.3 Criteria for study hold due to adverse events	The criteria have been amended to align with the European Medicines Agency Guidance on risk mitigation in first-in-human and early clinical trials.	Regulatory alignment

Section # and Name	Description of Change	Brief Rationale
Section 8.5.5 Pregnancy	The pregnancy language was updated that UCB will collect pregnancy and birth information for up to 12 months after a birth. This aligns with other PSL protocols.	Correction and alignment with other PSL protocols

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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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