AN OPEN-LABEL, RANDOMIZED, TWO-WAY CROSSOVER STUDY TO INVESTIGATE THE POTENTIAL PHARMACOKINETIC INTERACTION OF PADSEVONIL WITH ORAL CONTRACEPTIVES IN HEALTHY FEMALE PARTICIPANTS

PROTOCOL UP0035 AMENDMENT 2

PHASE 1

Short title:

A pharmacokinetic, safety, and tolerability study of the interaction of padsevonil and oral contraceptives in healthy female participants.

Sponsor:
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Regulatory agency identifying number(s):

IND Number:	135622
EudraCT Number	2019-002194-54

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 2	25 Feb 2020	Substantial
Protocol Amendment 1	10 Oct 2019	Substantial
Original Protocol	01 Aug 2019	Not applicable

Amendment 2 (25 Feb 2020)

Overall Rationale for the Amendment

The study was temporarily placed on hold after the protocol-defined criteria were met (Section 7.2) ie, 2 severe adverse events (AEs) were reported in 2 study participants. Protocol Amendment 2 is to restart the study and includes a reduction in the dose of padsevonil (PSL) from 400mg BID to 200mg BID.

During the study, a group of 14 study participants experienced central nervous system (CNS) AEs that were expected in type, but which in some study participants were less well tolerated than by study participants dosed at the same 400mg BID level in other ongoing healthy volunteer studies. In 1 study participant, these AEs (Verbatim Terms: [redacted]) were transiently of severe intensity on the 8th day of dosing at 400mg BID, while another study participant experienced withdrawal effects that were also of severe intensity over the first 2 days following completion of the taper. No study participants were prematurely withdrawn from the study.

The PSL dose of 400mg BID in UP0035 is one that has been well tolerated in ongoing studies in epilepsy patients, where more extended titration and tapering schedules are followed. Compared with other clinical pharmacology studies with PSL, the duration of treatment in this study is considerably longer, and it is likely that this contributed to the persistent AEs.

It has been decided to reduce the maximum PSL dose level from 400mg BID to 200mg BID and reduce the duration of dosing from 19 days to 11 days for subsequent study participants (through significant shortening of titration and taper period). The total exposure (cumulative PSL dose in mg) will be significantly reduced and similar to other ongoing clinical pharmacology studies. This is expected to reduce the AE burden on study participants and to reduce the likelihood of withdrawals. It is the evaluation of the Sponsor that the data collected in the study to date, coupled with the data generated following this reduction will still enable attainment of the drug-drug interaction (DDI) objectives of the study. As an additional safety precaution, the Safety Follow-up Period in the newly added Part 2 has also been extended from a maximum of 10 to a maximum of 14 days from last dose of study medication after each Treatment Sequence.

Section # and Name	Description of Change	Brief Rationale
Title page	Sponsor name has been updated from SPRL to SRL.	Belgium has recently adopted a new Code of Companies and Associations, resulting in a mandatory change of the name of the legal form of the entity "*société privée à responsabilité limitée*", abbreviated "*SPRL*", to "*société à responsabilité limitée*", abbreviated "*SRL*". This change does not involve any change to the legal form itself, and the company name, company number and VAT number of UCB Biopharma remain the same.
Section 1.1.4 and Section 3, Objectives and endpoints	-Where PSL dose is specified as 400mg BID in the objective, 200mg BID has also been added. -Secondary endpoint, "Incidence of AEs and SAEs" has been revised to "Incidence of TEAEs and SAEs".	-200mg BID will be the maximum PSL dose evaluated in Part 2 of the study. -Clarification.
Section 1.1.5 and Section 3, Overall design and Section 4, Study design	Part 2 has been added and described. The original design has now been designated Part 1. The number of study participants who have completed Part 1 at the time of its closure and replacement with Part 2 has been specified. The timing of the SFU visit in Part 1 has been corrected. The Part 2 description includes the key elements of a reduction in PSL treatment duration and extension of the SFU Period. The number of study participants planned in Part 2 has been specified.	For Part 2, see overall rationale for the amendment. The SFU Day range for Part 1 was corrected so that it is consistent with the text in Section 1.1.7, Treatment groups and duration, which states, the SFU Visit should occur no sooner than 7 days, and at a maximum of 10 days following the final dose of study medication.
Section 1.2, Schema	A study schematic for Part 2 (Table 1-3) has been added. The original schema (Table 1-2) has been retitled as Part 1 treatment sequences, and SFU Day has been corrected.	See overall rationale for the amendment. The SFU/EOS day for Part 1 was corrected for reason previously provided.
Section 1.3, Schedule of Activities	Schedules of study activities for Part 2, Treatment Sequence A (Table 1-6) and	See overall rationale for the amendment.

Section # and Name	Description of Change	Brief Rationale
	Part 2, Treatment Sequence B (Table 1-7) have been added. The original Schedules have been retitled to specify that they apply to Part 1.	
Section 1.3.1.1, Table 1-4, Schedule of activities – Part 1 Treatment Sequence A	-EOS/SFU/EDV Day corrected -General medical/medications/procedures history added to Baseline, Day -1 -Several assessments moved from Day 34 to Day 33 (1 day prior to OC dosing for the OC-only Period) -Row for Discharge added -Discharge at start of Washout extended by 1 day at discretion of PI (Footnote i added). -Footnote h clarified to specify collection only of Mitra™ samples (not venous blood samples).	Clarification.
Section 1.3.1.2, Table 1-5, Schedule of activities – Part 1 Treatment Sequence B	-EOS/SFU/EDV Day corrected -General medical/medications/procedures history added to Baseline, Day -1 -Several assessments moved from Day 18 to Day 17 (one day prior to PSL dosing in the PSL+OC Period) -Footnote e removed from 12-lead ECG assessment on Day 30. -Footnote e was corrected. Deleted Day 30 and added Day 29. -Physical examination, labs, and ECG added to Day 36. -Row for Discharge added. -Discharge added to Day 3 -Discharge at start of SFU Period extended by 1 day at discretion of PI (Footnote i added). -Footnote c clarified. No physical exam on Days 24 to 28. -Footnotes pertaining to PK sampling have been revised to remove redundancy and to remove PSL sample at 36h. -Footnote h (Previously footnote i) clarified to specify only the collection	Clarification.

Section # and Name	Description of Change	Brief Rationale
	of Mitra™ samples (not venous blood samples).	
Section 2.3, Benefit/risk assessment	The benefit/risk assessment has been revised.	The revision was needed to account for the TEAEs which triggered study hold and the addition of Part 2, with its essential features of a reduction in duration of PSL dosing and an extended SFU Period.
Section 4.2, Scientific rationale for study design	Revisions have been made that are necessitated by the reduction of the maximum PSL dose from 400mg BID in Part 1 to 200mg BID in Part 2.	See overall rationale for the amendment.
Section 4.3, Justification for dose	Justification has been provided for reduction of the maximum PSL dose from 400mg BID in Part 1 to 200mg BID in Part 2, including UCB's assessment that the objective to explore the potential DDI between PSL and OC will not be compromised by the dose reduction.	See overall rational for the amendment.
Section 5.2, Exclusion criterion 7	-Specified that the criterion pertains to Screening. -Added that if blood pressure results on Baseline (Day -1) are deemed clinically significant by the principal investigator or designee, the study participant will not be included.	Correction/clarification.
Section 5.2, Exclusion criterion 14	Specified that the C-SSRS completed at Baseline (Day -1) is the "Since Last Visit" version.	Clarification.
Section 5.3.1, Meals and dietary restrictions; Section 6.1, Treatments administered	Specified that on PK sampling days, study participants should remain semi-recumbent until 4 hours after the morning dose of PSL.	Clarification.
Section 6.3, Measures to minimize bias: randomization and blinding	Deleted reference to "code break envelopes" and "sealed envelopes."	Inclusion of this text was an oversight. This is an open-label study.
Section 6.5.1, Permitted concomitant treatments (medications and therapies)	The example of "hormonal contraceptives" as a concomitant medication that could be taken if approved on a case-by-case basis prior to enrollment has been deleted.	It is not an appropriate example, because study participants can't take OCs apart from study OCs.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.2, QTc stopping criteria	Signs for QTc and QTc change from baseline corrected from > to ≥.	Correction.
Section 7.2, Criteria for study hold due to adverse events	-The severe nonserious adverse reaction criterion has been revised to specify that the criterion is triggered by occurrence in 2 study participants in Part 1 or Part 2 of the study. -Specified that tapering of PSL doses and the completion of the OC-only TreatmentPperiod in Sequence A will be allowed.	This is necessitated by the stoppage of Part 1 and the division of the study into 2 parts. It will ensure that Part 2 study participants receive the same degree of protection as those in Part 1.
Section 8.1.1, Mitra™	Revisions have been made to specify the target number of study participants in each part from which Mitra™ samples will be collected.	Additional Mitra™ samples are required to fulfill the objective.
Section 8.10, Samples for PSL bioanalytical method cross-validation	Minor revisions have been made to wording and to the name of the report.	Clarification.
Section 9.3, Planned pharmacokinetic analyses	-Specified that PK analyses will be performed and reported for each study part. -The criteria for lack of clinically significant interaction between PSL and OC have been further specified. -Study days for which PK parameters will be compared have been specified for Part 2.	-This is necessitated by the addition of Part 2. -This is to allow more flexibility in the interpretation the clinical significance of the PK interaction. -This is necessitated by the addition of Part 2, which does not match Part 1 in terms of treatment days (due to shortening of PSL treatment duration).
Section 9.4, Planned safety analyses	-Specified that safety variables will be listed and summarized by study part. -Specified that safety variables will be listed and summarized for PSL treatment alone, ie, prior to administration of OC in the PSL+OC Period.	-This is necessitated by the addition of Part 2. -This was not previously specified.
Section 9.9, Determination of sample size	This has been revised to account for discontinuation of Part 1 before the planned 20 study participants were enrolled and to describe the power	This was necessitated by the addition of Part 2.

Section # and Name	Description of Change	Brief Rationale
	associated with the planned 26 study participants in Part 2.	
Section 10.2, Appendix 2: Clinical Laboratory Tests and Section 10.4.2.2, Pregnancy testing	Revised to reflect that all pregnancy tests in the study are serum pregnancy tests rather than urine pregnancy tests.	Clarifications to the nonapplicable text of standard protocol template appendices.
Section 10.10, Appendix 10: Abbreviations and trademarks	New abbreviations have been added.	Standard procedure.

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; C-SSRS=Columbia Suicide Severity Rating Scale; EDV=Early Discontinuation Visit; EOS=End of Study; h=hour(s); OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; QTc=QT interval corrected for heart rate; SFU=Safety Follow-up; TM=registered trade mark; VAT=value added tax

SERIOUS ADVERSE EVENT REPORTING

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

1.1.1 Protocol title:

An open-label, randomized, two-way crossover study to investigate the potential pharmacokinetic interaction of padsevonil with oral contraceptives in healthy female participants.

1.1.2 Short title:

A pharmacokinetic, safety, and tolerability study of the interaction of padsevonil with oral contraceptives in healthy female participants.

1.1.3 Rationale:

Padsevonil is currently being investigated for the treatment of focal onset seizures in adult patients with drug-resistant epilepsy. Preclinical investigations (NCD2151, NCD2356), which used cryopreserved human hepatocytes, showed that PSL was a weak CYP3A4 inducer. These in vitro findings were confirmed in a clinical drug-drug interaction (DDI) study (UP0013) with midazolam, a sensitive CYP3A4 probe substrate, which showed that PSL given at 400mg twice daily (BID) over 6 days, reduced the oral exposure of midazolam by 44%. Oral contraceptives (OC), usually in the form of fixed combinations of estrogen and progestin steroids, are metabolized at the gut and hepatic level (via oxidation by CYP3A4) (Zhang et al, 2018). Therefore, there is potential for PSL to decrease the exposure of OC, and thus impair their effectiveness.

This study aims to evaluate the effect of the likely impact of coadministration of PSL on the exposure of ethinylestradiol (EE) and levonorgestrel (LN). The outcome of this study will be used to inform labeling regarding the use of PSL in combination with OC.

1.1.4 Objectives and endpoints

Table 1-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To investigate the effect of steady-state PSL (400mg BID or 200mg BID) on the PK of a single dose oral contraceptive containing EE 30µg and LN 150µg.	– C_{max} and AUC of EE and LN
Secondary	
• To evaluate the safety and tolerability of PSL in healthy female study participants.	– Incidence of TEAEs and SAEs
• To evaluate the effect of single-dose oral contraceptive containing EE 30µg and LN 150µg on the steady-state PK of PSL.	– $C_{max(ss)}$ and AUC_{τ} of PSL

Table 1-1: Objectives and endpoints

Objectives	Endpoints
Other	
• To evaluate the safety and tolerability of PSL in healthy female study participants.	– Changes in vital signs (oral or aural temperature, pulse rate, respiratory rate, and BP) – Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis) – Changes in 12-lead ECG assessments – Physical and neurological examination findings
• To evaluate the effect of a single-dose oral contraceptive containing EE 30µg and LN 150µg on the steady-state PK of PSL.	– CL_{ss}/F, C_{min}, t_{max}, $t_{1/2}$ of PSL
• To evaluate the effect of a single-dose oral contraceptive containing EE 30µg and LN 150µg on the steady-state PK of PSL metabolites	– AUC_{τ} and $C_{max,ss}$, t_{max}, $t_{1/2ss}$, C_{trough}, and metabolic ratios of AUC_{τ} and $C_{max,ss}$
• To investigate the effect of steady-state PSL (400mg BID or 200 mg BID) on the PK of a single-dose oral contraceptive containing EE 30µg and LN 150µg	– T_{max}, $AUC_{(0-t)}$, $t_{1/2}$,and CL/F of EE and LN
• To collect and store blood samples for genotyping of drug metabolizing enzymes and/or transporters. (if needed)	– Potential genotyping of study participants for specific genes related to drug metabolizing enzymes and/or transporters.
• To collect venous plasma and blood samples (Mitra™) for cross-validation of PSL bioanalytical method	– Cross validation of PSL bioanalytical method.

BP=blood pressure; ECG=electrocardiogram; EE=ethinylestradiol; LN= levonorgestrel PK=pharmacokinetic; PSL=padsevonil; SAE=serious adverse event; TEAE=treatment-emergent adverse event

1.1.5 Overall design

This is a Phase 1, open label, randomized, 2-way cross-over study to investigate the potential pharmacokinetic (PK) interaction of PSL with OC in healthy female study participants.

Prior to Protocol Amendment 2, the intention was to screen a sufficient number of study participants to ensure that 20 study participants would be included in each treatment sequence shown in Table 1-2. This pair of treatment sequences has now been designated as Part 1, necessitated by the introduction of a new pair of treatment sequences at the new, lower

dose level, termed Part 2, for new study participants that will be enrolled under the amended protocol. At the time of Amendment 2, 14 study participants completed Part 1 and were dosed with PSL 400mg BID (7 study participants in Sequence A and 7 study participants in Sequence B). In Part 2, a sufficient number of study participants will be screened to ensure that 13 study participants are included in each treatment sequence.

Each Part of the study (1 and 2) consists of a Screening Visit, 2 Treatment Periods with at least a 14-day washout between periods, and a Safety Follow-up (SFU) Visit that will occur no sooner than 7 days, and at a maximum of 10 days (Part 1) or 14 days (Part 2) following the final dose of study medication.

Study participants who provide written informed consent will be screened during the 28-day period from Day -29 to Day -2. Study participants who meet all inclusion and none of the exclusion criteria will check into the clinic on Day -1 (Baseline, the day prior to Day 1, the first day of the first Treatment Period, and will be randomized into one of the 2 treatment sequences: Treatment Sequence A or Treatment Sequence B (see Section 1.3, Schedules of activities).

Each study participant will be dosed with OC and OC+PSL during the 2 Treatment Periods in either Treatment Sequence A or Treatment Sequence B. If the study participant is randomized to Treatment Sequence A, they will receive OC+PSL during the first Treatment Period followed by OC alone during second Treatment Period. If the study participant is randomized to Treatment Sequence B, they will receive OC alone during the first Treatment Period followed by OC+PSL during the second Treatment Period. There will be a Washout Period of at least 14 days between treatments within each sequence (see Section 1.2, Schema).

Part 1

Sequence A

Study participants enrolled in the Treatment Sequence A group will start with up-titration of PSL with increasing repeated BID doses to reach a steady-state dose level of PSL 400mg BID. Once at steady-state, on the morning of Day 13, study participants will receive a single dose of OC in addition to PSL 400mg BID. From Day 15 to Day 19, PSL will be tapered from a dose of 400mg BID to 100mg BID. On Day 20, study participants will start the 14-day Washout Period. On Day 34, a single dose of OC will be administered followed by 2 days of PK measurements. An SFU Visit will occur between Day 41 to Day 44.

Sequence B

Study participants enrolled in the Treatment Sequence B group will start with the single dose of OC on the morning of Day 1 followed by 2 days of PK measurements and will then start the 14-day Washout Period. At the end of the Washout Period, the Treatment Sequence B group will start with up-titration of PSL treatment with increasing repeated BID doses to reach a steady-state dose level of PSL 400mg BID. Once at steady-state, on the morning of Day 30, study participants will receive a single dose of OC in addition to PSL 400mg BID. From Day 32 to Day 36, PSL will be tapered from a dose of 400mg BID to 100mg BID. All study participants will complete an SFU Visit between Day 43 and Day 46.

Part 2

Protocol Amendment 2 introduces Part 2 (Schematic shown in Table 1-3) in which 26 study participants are planned to be enrolled, due to the stop of Part 1 after the completion of 14 study participants.

Sequence A

All study participants enrolled in Part 2, Treatment Sequence A, will be administered PSL 100mg BID on Day 1, with titration to 200mg BID for Day 2 to Day 10. A single dose of OC is administered on the morning of Day 9, at which time PSL is at steady state. Pharmacokinetic assessments will be collected according to the Schedule of Activities. To taper, 100mg BID of PSL will be given on Day 11. Starting on Day 12, the study participants will then complete a Washout Period for 14 days followed by a return to the clinic on Day 25 for the OC-only dosing on Day 26. Pharmacokinetic samples will be collected on Days 26, 27, and 28. An SFU Visit will occur between Day 33 and Day 40.

Sequence B

All study participants enrolled in Part 2, Treatment Sequence B, will be administered a single dose of OC on the morning of Day 1 followed by PK assessments that day and the next 2 days. The study participants will then complete a 14-day Washout Period followed by a return to the clinic for the OC+PSL dosing from Day 18 to Day 28 (OC to be administered on Day 26, at which time PSL is at steady state). Study participants will be administered PSL 100mg BID on Day 18, with titration to 200mg BID for Day 19 to Day 27. To taper, 100mg BID of PSL will be given on Day 28. An SFU Visit will occur between Day 35 and Day 42.

1.1.6 Number of study participants

Forty evaluable study participants will be enrolled overall. A total of 14 evaluable study participants (7 study participants in each sequence) have completed Part 1 with PSL 400mg BID dosing. For Part 2 with PSL 200mg BID dosing, a total of 26 evaluable study participants is planned (13 study participants in each sequence).

Study participants who are withdrawn may be replaced following discussion between the Investigator and Sponsor.

1.1.7 Treatment groups and duration

In Part 1, the maximum total duration of the study is approximately 75 days for each study participant, including the Screening Period (up to 28 days), a 36-day Treatment Period including a 14-day Washout Period, and a SFU Visit (the SFU Visit should occur no sooner than 7 days, and at a maximum of 10 days following the final dose of study medication). Study participants in Part 1 (either sequence) will be treated with PSL (maximum dose of 400mg BID) for a total of 19 days.

In Part 2, the maximum total duration of the study is approximately 70 days for each study participant, including the Screening Period (up to 28 days), a 28-day Treatment Period, including a 14-day Washout Period, and a SFU Visit (the SFU Visit should occur no sooner than 7 days, and at a maximum of 14 days following the final dose of study medication). Study participants in Part 2 (either sequence) will be treated with PSL (maximum dose of 200mg BID) for 11 days, a reduction of 8 days compared with Part 1.

1.2 Schema

Detailed schematic diagrams of the Part 1 and Part 2 treatment sequences are provided in Table 1-2 and Table 1-3.

Table 1-2: Part 1 treatment sequences

Part 1 Treatment Sequence A

	PSL+OC									Washout (14 Days)	OC			SFU/ EOS
Day	**1**	**2 to 3**	**4 to 5**	**6 to 12**	**13**	**14**	**15 to 16**	**17 to 18**	**19**	**20 to 33**	**34**	**35**	**36**	**41 to 44**
OC Dose					OC SD						OC SD			
PSL Dose (mg)	100 BID	200 BID	300 BID	400 BID	400 BID	400 BID	300 BID	200 BID	100 BID					
PK Sampling		PK (Day 2 only)[a]	PK (Day 4 only) [a]	PK (Days 6, 8, 10, and 12)	PK	PK	PK (Day 15 only)				PK	PK	PK	

Part 1 Treatment Sequence B

	OC			Washout (14 Days)	PSL+OC								SFU/ EOS
Day	**1**	**2**	**3**	**4 to 17**	**18**	**19 to 20**	**21 to 22**	**23 to 29**	**30**	**31**	**32 to 33**	**34 to 35**	**36**	**43 to 46**
OC Dose	OC SD								OC SD					
PSL Dose(mg)					100 BID	200 BID	300 BID	400 BID	400 BID	400 BID	300 BID	200 BID	100 BID	
PK Sampling	PK	PK	PK			PK (Day 19 only) [a]	PK (Day 21 only) [a]	PK (Days 23, 25, 27, and 29)	PK	PK	PK (Day 32)			

BID=twice daily; EOS=End of Study; OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; SD=single dose; SFU=Safety Follow-up
[a] Pharmacokinetic samples must be taken before morning dose of PSL.

Table 1-3: Part 2 treatment sequences

Part 2 Treatment Sequence A

	PSL+OC					Washout (14 Days)	OC			SFU/ EOS
Day	**1**	**2 to 8**	**9**	**10**	**11**	**12 to 25**	**26**	**27**	**28**	**33 to 40**
OC Dose			OC SD				OC SD			
PSL Dose (mg)	100 BID	200 BID	200 BID	200 BID	100 BID					
PK Sampling		PK (Days 2, 4, 6, 8 only) [a]	PK	PK	PK		PK	PK	PK	

Part 2 Treatment Sequence B

	OC			Washout (14 Days)	PSL+OC					SFU/ EOS
Day	**1**	**2**	**3**	**4 to 17**	**18**	**19 to 25**	**26**	**27**	**28**	**35 to 42**
OC Dose	OC SD						OC SD			
PSL Dose (mg)					100 BID	200 BID	200 BID	200 BID	100 BID	
PK Sampling	PK	PK	PK			PK (Day 19, 21, 23, 25 only) [a]	PK	PK	PK	

BID=twice daily; EOS=End of Study; OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; SD=single dose; SFU=Safety Follow-up
[a] Information on sampling time is provided in the Schedule of Activities Table.

1.3 Schedule of Activities

The Schedules of Activities for Part 1, Treatment Sequences A and B are presented in Table 1-4 and Table 1-5, respectively.

The Schedules of Activities for Part 2, Treatment Sequences A and B are presented in Table 1-6 and Table 1-7, respectively.

1.3.1 Part 1

1.3.1.1 Part 1 Sequence A

Table 1-4: Schedule of activities- Part 1 Treatment Sequence A

	Screening	Baseline	OC+PSL									Washout (14 Days)	OC			EOS/ SFU/ EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2 to 3**	**4 to 5**	**6 to 12**	**13**	**14**	**15 to 16**	**17 to 18**	**19**	**20 to 33**	**34**	**35**	**36**	**41 to 44**
Written informed consent	X															
Demographics and baseline characteristics	X															
Inclusion /Exclusion criteria verification	X	X	X													
General medical /medications/ procedures history	X	X										X (D33)				
Suicidality Risk Assessment (C-SSRS)[b]	X	X										X (D33)				X
Psychiatric and mental status evaluation	X	X	X	X	X	X	X	X	X	X	X					X
Physical examination[c]	X	X	X			X					X	X (D33)				X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Pregnancy test	X	X										X (D33)				
Hematology, clinical chemistry, urinalysis	X	X									X	X (D33)				X
Serology (HIV, HBsAg HEV, syphilis, and HCV-Ab)	X															

Table 1-4: Schedule of activities- Part 1 Treatment Sequence A

	Screening	Baseline	OC+PSL									Washout (14 Days)	OC			EOS/ SFU/ EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2 to 3**	**4 to 5**	**6 to 12**	**13**	**14**	**15 to 16**	**17 to 18**	**19**	**20 to 33**	**34**	**35**	**36**	**41 to 44**
12-lead ECG	X	X	X	X[e]	X[e]	X[e]	X	X			X					X
Urine and cotinine drug screen, and alcohol breath test	X	X										X (D33)				
Recording of adverse events/medical procedures	X	X	X	X	X	X	X	X	X	X	X	X (D33)	X	X	X	X
Blood sampling for genotyping of drug metabolizing enzymes and/or transporters		X														
Admit to clinic		X										X (D33)				
Administer PSL			X	X	X	X	X	X	X	X	X					
Administer OC							X						X			
Blood sampling for PSL PK levels				X[f]	X[f]	X[f]	X[f]	X[f]	X[f]							
Blood sampling for OC PK levels							X[g]	X[g]	X[g]				X[g]	X[g]	X[g]	
Blood sampling for cross-validation[h]						X										
Discharge												X (D20 or D21)[i]			X	

C-SSRS=Columbia Suicide Severity Rating Scale; EOS=End of Study; EDV=Early Discontinuation Visit; ECG=electrocardiogram; h=hour(s); HbsAg-Ab=HepB surface antigen antibodies; HCV-Ab=HepC virus antibodies; HEV=hepatitis E virus; HIV=human immunodeficiency virus; OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; SFU=Safety Follow-Up

[a] If a study participant discontinues early, SFU procedures should be completed as the EDV. Upon early termination/withdrawal, the study participant will be encouraged to complete SFU assessments following the last dose of study medication.
[b] All study participants will complete the "Screening/Baseline" version of the C-SSRS during Screening (assessing the past 6 months), followed by the "Since Last Visit" version at subsequent visits.
[c] At Screening, Baseline (Day -1), Day 6, and Day 12, a full physical examination will be performed. On all other days a physical examination is performed, it will be a brief physical examination (Section 8.3.1). On Days 7 to 11, physical examination will not be performed.
[d] Oral or aural body temperature (temperature must be performed using the same method in any individual study participant on all occasions), pulse rate, respiratory rate, and blood pressure will be assessed. Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement.
[e] ECG will be completed on Days 2, 4, 6, and 12 only of multiple day periods during Treatment Sequence A.
[f] During the OC+PSL Treatment Period, trough levels of PSL will be collected on morning before PSL dosing on Day 2, Day 4, Day 6, Day 8 and Day 10. Additional blood sampling for PK analysis will be taken on Day 12 (PSL PK) before (predose) and after PSL morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h postdose and on Day 13 (PSL and OC PK) before (predose) and after the PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (before morning PSL dose on Day 14), and 48h (before morning PSL dose on Day 15) postdose.
[g] During OC+PSL Treatment Period, blood sampling for OC PK analysis will be taken on Day 13 (before OC+PSL morning dose) and after PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 14), 36h (Day 14), and 48h (Day 15) postdose. During the single-dose OC period, PK blood samples will be taken on Day 34 at predose and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 35), 36h (Day 35), and 48h (Day 36) postdose.
[h] Mitra ™ (finger prick) blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 12 only for selected study participants. See Section 8.1.1 for details about selection.
[i] The study participant can be discharged on Day 20 or Day 21, at the discretion of the principal investigator.

1.3.1.2 Part 1 Sequence B

Table 1-5: Schedule of activities- Part 1 Treatment Sequence B

	Screening	Baseline	OC			Washout (14 Days)	PSL+OC									EOS/ SFU EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4 to 17**	**18**	**19 to 20**	**21 to 22**	**23 to 29**	**30**	**31**	**32 to 33**	**34 to 35**	**36**	**43 to 46**
Written informed consent	X															
Demographics and baseline characteristics	X															
Inclusion /Exclusion criteria verification	X	X	X				X									
General medical /medications/ procedures history	X	X				X (D17)										
Suicidality Risk Assessment (C-SSRS)[b]	X	X				X (D17)										X
Psychiatric and mental status evaluation	X	X					X	X	X	X	X	X	X	X	X	X
Physical examination[c]	X	X					X			X					X	X
Vital signs[d]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test	X	X				X (D17)										
Hematology, clinical chemistry, urinalysis	X	X				X (D17)									X	X
Serology (HIV, HbsAg, HEV, syphilis, and HCV-Ab)	X															
12-lead ECG	X	X	X				X	X[e]	X[e]	X[e]	X	X			X	X

Table 1-5: Schedule of activities- Part 1 Treatment Sequence B

	Screening	Baseline	OC			Washout (14 Days)	PSL+OC								EOS/ SFU EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4 to 17**	**18**	**19 to 20**	**21 to 22**	**23 to 29**	**30**	**31**	**32 to 33**	**34 to 35**	**36**	**43 to 46**
Urine and cotinine drug screen, and alcohol breath test	X	X				X (D17)										
Recording of adverse events/medical procedures	X	X	X	X	X	X(D17)	X	X	X	X	X	X	X	X	X	X
Blood sampling for genotyping of drug metabolizing enzymes and/or transporters		X														
Admit to clinic		X				X (D17)										
Administer PSL							X	X	X	X	X	X	X	X	X	
Administer OC			X								X					
Blood sampling for PSL PK levels								X[f]	X[f]	X [f]	X[f]	X[f]	X[f]			
Blood sampling for OC PK levels			X[g]	X[g]	X[g]						X[g]	X[g]	X[g]			
Blood sampling for cross-validation[h]										X						
Discharge					X											X (D37 or D38)[i]

C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EDV= Early Discontinuation Visit; EOS=End of Study; h=hour(s); HbsAg-Ab=HepB surface antigen antibodies; HCV-Ab=HepC virus antibodies; HEV=hepatitis E virus; HIV=human immunodeficiency virus; OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; SFU=Safety Follow-Up

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

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

[c] At Screening, Baseline (Day -1), Day 23, and Day 29, a full physical examination will be performed. On all other days a physical examination is performed, it will be a brief physical examination (Section 8.3.1). On days 24-28, physical examination will not be performed.

[d] Oral or aural body temperature (temperature must be performed using the same method in any individual study participant on all occasions.), pulse rate, respiratory rate, and blood pressure will be assessed. Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement.

[e] ECG will be completed on Days 19, 21, 23, and 29 only of multiple day periods during Treatment Sequence B.

[f] During the OC+PSL Treatment Period, trough levels of PSL will be collected on morning before PSL dosing on Day 19, Day 21, Day 23, Day 25, and Day 27. Additional blood sampling for PK analysis will be taken on Day 29 (PSL PK) before (predose) and after PSL morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h postdose and on Day 30 (PSL PK) before (predose) and after the PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h postdose. In addition, blood samples will be obtained prior to the morning dose on Day 31 and prior to the morning dose on Day 32.

[g] During the single-dose OC period, PK blood samples will be taken on Day 1 at predose and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day2), 36h (Day 2), and 48h (Day 3) postdose. During OC+PSL Treatment Period, blood sampling for OC PK analysis will be taken on Day 30 (before OC+PSL morning dose) and after PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 31), 36h (Day 31), and 48h (Day 32) postdose.

[h] Mitra ™ (finger prick) blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 29 only. See Section 8.1.1 for details about selection.

[i] The study participant can be discharged on Day 37 or Day 38, at the discretion of the principal investigator.

1.3.2 Part 2

1.3.2.1 Part 2 Sequence A

Table 1-6: Schedule of activities- Part 2 Treatment Sequence A

	Screening	Baseline	OC+PSL					Washout (14 Days)	OC			EOS/ SFU/ EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2 to 8**	**9**	**10**	**11**	**12 to 25**	**26**	**27**	**28**	**33 to 40**
Written informed consent	X											
Demographics and baseline characteristics	X											
Inclusion /Exclusion criteria verification	X	X	X									
General medical /medications/ procedures history	X	X						X (D25)				
Suicidality Risk Assessment (C-SSRS)[b]	X	X						X(D25)				X
Psychiatric and mental status evaluation	X	X	X[h]	X[h]	X[h]	X[h]	X[h]					X
Physical examination[c]	X	X	X	X			X	X (D25)				X
Vital signs[d]	X	X	X	X	X	X	X		X	X	X	X
Pregnancy test	X	X						X (D25)				
Hematology, clinical chemistry, urinalysis	X	X					X	X (D25)				X
Serology (HIV, HBsAg HEV, syphilis, and HCV-Ab)	X											
12-lead ECG	X	X	X	X[e]	X	X	X					X

Table 1-6: Schedule of activities- Part 2 Treatment Sequence A

	Screening	Baseline	OC+PSL					Washout (14 Days)	OC			EOS/ SFU/ EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2 to 8**	**9**	**10**	**11**	**12 to 25**	**26**	**27**	**28**	**33 to 40**
Urine and cotinine drug screen, and alcohol breath test	X	X						X (D25)				
Recording of adverse events/medical procedures	X	X	X	X	X	X	X	X (D25)	X	X	X	X
Blood sampling for genotyping of drug metabolizing enzymes and/or transporters		X										
Admit to clinic		X						X (D25)				
Administer PSL			X	X	X	X	X					
Administer OC					X				X			
Blood sampling for PSL PK levels				X[f]	X[f]	X[f]	X[f]					
Blood sampling for OC PK levels					X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	
Blood sampling for cross-validation[j]				X								
Discharge								X (D12 or D13)[i]			X	

C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EOS=End of Study; h=hour(s); HbsAg-Ab=HepB surface antigen antibodies; HCV-Ab=HepC virus antibodies; HEV=hepatitis E virus; HIV=human immunodeficiency virus; OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; SFU=Safety Follow-Up

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

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

[c] At Screening, Baseline (Day -1), and Day 8, a full physical examination will be performed. On all other days a physical examination is performed, it will be a brief physical examination (Section 8.3.1). On days 2-7, physical examination will not be performed.

[d] Oral or aural body temperature (temperature must be performed using the same method in any individual study participant on all occasions), pulse rate, respiratory rate, and blood pressure will be assessed. Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement.

[e] ECG will be completed on Days 2, and 8 only of multiple day periods during Treatment Sequence A.

[f] During the OC+PSL Treatment Period, trough levels of PSL will be collected on morning before PSL dosing on Day 2, Day 4, and Day 6. Additional blood sampling for PK analysis will be taken on Day 8 before (predose) and after PSL morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h postdose and on Day 9 before (predose) and after the PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (before morning PSL dose on Day 10), and 48h (before morning PSL dose on Day 11) postdose.

[g] During OC+PSL Treatment Period, blood sampling for OC PK analysis will be taken on Day 9 (before OC+PSL morning dose) and after PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, In addition, blood samples will be obtained prior to the morning dose on Day 10, 36h (Day 10), and 48h (Day 11) postdose. During the single-dose OC period, PK blood samples will be taken on Day 26 at predose and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 27), 36h (Day 27), and 48h (Day 28) postdose.

[h] Psychiatric and mental status evaluation will be done pre-dose.

[i] The study participant can be discharged on Day 12 or Day 13, at the discretion of the principal investigator.

[j] Mitra ™ (finger prick) and venous blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 8 only for selected study participants. See Section 8.1.1 for details about selection.

1.3.2.2 Part 2 Sequence B

Table 1-7: Schedule of activities- Part 2 Treatment Sequence B

	Screening	Baseline	OC			Washout (14 Days)	PSL+OC					EOS/ SFU EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4 to 17**	**18**	**19 to 25**	**26**	**27**	**28**	**35 to 42**
Written informed consent	X											
Demographics and baseline characteristics	X											
Inclusion /Exclusion criteria verification	X	X	X				X					
General medical /medications/ procedures history	X	X				X (D17)						
Suicidality Risk Assessment (C-SSRS)[b]	X	X				X (D17)						X
Psychiatric and mental status evaluation	X	X					X[f]	X[f]	X[f]	X[f]	X[f]	X
Physical examination[c]	X	X					X	X			X	X
Vital signs[d]	X	X	X	X	X		X	X	X	X	X	X
Pregnancy test	X	X				X (D17)						
Hematology, clinical chemistry, urinalysis	X	X				X(D17)					X	X
Serology (HIV, HbsAg, HEV, syphilis, and HCV-Ab)	X											
12-lead ECG	X	X	X				X	X[e]	X	X	X	X

Table 1-7: Schedule of activities- Part 2 Treatment Sequence B

	Screening	Baseline	OC			Washout (14 Days)	PSL+OC					EOS/ SFU EDV[a]
Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4 to 17**	**18**	**19 to 25**	**26**	**27**	**28**	**35 to 42**
Urine and cotinine drug screen, and alcohol breath test	X	X				X(D17)						
Recording of adverse events/medical procedures	X	X	X	X	X	X (D17)	X	X	X	X	X	X
Blood sampling for genotyping of drug metabolizing enzymes and/or transporters		X										
Admit to clinic		X				X (D17)						
Administer PSL							X	X	X	X	X	
Administer OC			X						X			
Blood sampling for PSL PK levels								X[g]	X[g]	X[g]	X[g]	
Blood sampling for OC PK levels			X[h]	X[h]	X[h]				X[h]	X[h]	X[h]	
Blood sampling for cross-validation[j]								X				
Discharge					X							X (D29 or D30)[i]

C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EOS=End of Study; h=hour(s); HbsAg-Ab=HepB surface antigen antibodies; HCV-Ab=HepC virus antibodies; HEV=hepatitis E virus; HIV=human immunodeficiency virus; OC=oral contraceptive; PK=pharmacokinetic; PSL=padsevonil; SFU=Safety Follow-Up

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

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

[c] At Screening, Baseline (Day -1), and Day 25, a full physical examination will be performed. On all other days a physical examination is performed, it will be a brief physical examination (Section 8.3.1). On Days 19-24, physical examination will not be performed.

[d] Oral or aural body temperature (temperature must be performed using the same method in any individual study participant on all occasions.), pulse rate, respiratory rate, and blood pressure will be assessed. Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement.

[e] ECG will be completed on Days 19, and 25 only of multiple day periods during Treatment Sequence B.

[f] Psychiatric and mental evaluation will be done pre-dose.

[g] During the OC+PSL Treatment Period, trough levels of PSL will be collected on morning before PSL dosing on Day 19, Day 21,and Day 23. Additional blood sampling for PK analysis will be taken on Day 25 before (predose) and after PSL morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h postdose and on Day 26 before (predose) and after the PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 27), and 48h (Day28) postdose.

h During the single-dose OC period, PK blood samples will be taken on Day 1 at predose and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 2), 36h (Day 2), and 48h (Day 3) postdose. During OC+PSL Treatment Period, blood sampling for OC PK analysis will be taken on Day 26 (before OC+PSL morning dose) and after PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 27), 36h (Day 27), and 48h (Day 28) postdose.

[i] The study participant can be discharged on Day 29 or Day 30, at the discretion of the principal investigator.

[j] Mitra ™ (finger prick) and venous blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 25 only for selected study participants. See Section 8.1.1 for details about selection.

2 INTRODUCTION

2.1 Study rationale

Padsevonil is a novel chemical entity with selective affinity for both presynaptic vesicle protein 2 (SV2) isoforms and postsynaptic central benzodiazepine receptor cBZR sites on the $GABA_A$ receptor that has shown compelling, broad-range efficacy in several preclinical models of epilepsy conducted by UCB. Padsevonil is currently being investigated for the treatment of focal onset seizures in adult patients with treatment-resistant epilepsy. Preclinical investigations (NCD2151, NCD2356), which used cryopreserved human hepatocytes, showed that PSL was a weak CYP3A4 inducer. These in vitro findings were confirmed in the clinical DDI study with midazolam, a sensitive CYP3A4 probe substrate (UP0013). Indeed, this study showed that PSL given at 400mg BID reduced the oral exposure of midazolam by 44%.

Oral contraceptives, usually in the form of fixed combinations of estrogen and progestin steroids, are metabolized via oxidation by CYP3A4 at the gut and hepatic level (Zhang et al, 2018). Strong CYP3A4 inducers like rifampin, carbamazepine, and phenytoin, which have very large impact on oral midazolam exposure (>80% exposure reduction), reduced the exposure of EE to a lesser extent (38% to 66%) (Backman et al, 1996). The smaller effect size of EE compared with oral midazolam to CYP3A4 inducers is most likely due to the multiple elimination pathways of EE which may be less inducible than CYP3A4. As a weak inducer of CYP3A4, it is expected that the effect of PSL on EE exposure will be less than that observed for oral midazolam. A fit-for-purpose physiologically-based PK model aiming at predicting the DDI between PSL and EE showed that a weak DDI (16% decrease of EE AUC) may occur at a PSL dose of 400mg BID.

Therefore, UP0035 aims to evaluate the impact of coadministration of PSL on the exposure of EE and LN. The outcome of this study will be used to inform labeling regarding the use of PSL in combination with OC.

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, paradoxical aggression), as well as the development of tolerance to anticonvulsant effects.

Compounds binding to SV2A proteins on synaptic vesicles are characterized by broad-spectrum efficacy against both generalized and partial seizures in preclinical models, and this protective activity strongly correlates with their binding affinity (Kaminski et al, 2008). The function of SV2B and SV2C subtypes is not well established, but they share a high degree of sequence homology to SV2A and localization within synaptic vesicles (Wan et al, 2010;

Janz and Südhof, 1999). Levetiracetam (LEV), exemplifying a SV2A-related mechanism of action, displays prominent clinical efficacy in patients with different forms of epilepsy (Klitgaard and Verdru, 2007).

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

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

2.3 Benefit/risk assessment

Overall, the AE profile of PSL in clinical pharmacology studies is consistent with the pharmacological activity of the product, and, as expected, in the context of early dose escalation studies in healthy study participants. The safety findings to date suggest that the AEs experienced by study participants receiving single and repeated doses of PSL are limited principally to 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.

As described in the Investigator's Brochure, the overall safety for the Phase 1 studies was generally good at doses up to 400mg BID administration. As of the cut-off date of 06 Dec 2019, there have been 2 serious adverse events (delirium and mania) and no deaths during the studies. Of the treatment emergent adverse events (TEAEs) occurring in 247 healthy study participants and 79 study participants with epilepsy exposed to PSL, 3 study participants reported 47 severe TEAEs, with the most prevalent being somnolence, fatigue and balance disorder. The severe psychiatric AEs that have occurred in Phase 1 and Phase 2 studies were delirium, depressed mood, and insomnia. These severe psychiatric adverse events were transient, and the symptoms resolved after withdrawal of PSL. The possibility of acute psychiatric AEs highlights the need to maintain vigilance for such effects and to monitor for any psychiatric/mood/behavioral signs in studies with healthy study participants and in studies with epilepsy patients.

Acute psychiatric events of transiently severe intensity were observed in 2 healthy study participants in UP0035. Such events are considered to be part of the identified risks of acute psychiatric incidents per the Safety Risk Management Strategy; ie, it is not unexpected for this type of event to occur, especially with repeated dosing at 400mg BID. The Safety Risk Management Strategy already considers that:

- Psychiatric and behavioral symptoms may require dose reduction or discontinuation.
- Study participants should be withdrawn if they develop psychiatric/mood/behavioral signs or disturbances that are 'clinically concerning' or that worsen over time.
- Clinically significant psychiatric AEs will lead to prompt withdrawal from studies.
- Monitoring for psychiatric AEs will be performed throughout the study and increased vigilance observed during dose titration and dose tapering, in addition to monitoring for withdrawal symptoms during dose taper of investigational medicinal product (IMP).

Unless compelled by objective-specific regulatory guidance, the clinical pharmacology studies have routinely used lower doses (ie, 200mg or 100mg) due to the poorer tolerability in healthy study participants as compared to epilepsy patients. However, in UP0035, such regulatory guidance was followed in order to evaluate the highest dose for potential effects of PSL on oral contraceptives. In addition, the dosing needed to be slightly longer versus other clinical pharmacology studies due to the time required for any induction of metabolizing enzymes by PSL to take place. The findings from this study will provide important information as to whether coadministration of PSL reduces exposure to EE and LN in women of child-bearing potential with epilepsy.

The nature, frequency and severity of the AEs are similar to those observed in earlier clinical pharmacology studies, even though some specific measures (titration and tapering) were utilized in this study to try to improve tolerability. This provides further evidence that healthy study participants do not tolerate repeated dosing of PSL at 400mg BID as well as epilepsy patients. It is currently unknown if a longer titration and tapering period would result in a better tolerability in healthy participants; nevertheless, this is not feasible for Phase 1 studies.

With respect to cardiovascular health, despite 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 (EP0069 and EP0073) 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 EP0069 and EP0073, and all echocardiograms were assessed as normal. There are currently no clinical data to suggest that the drug has an adverse effect on cardiovascular function other than a minimal lowering effect on blood pressure. The degrees of reduction seen in both systolic blood pressure and diastolic blood pressure are consistent with the GABA-A-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use. As a precaution, and in view of the nonclinical histopathological cardiac findings, echocardiogram screening of study participants at Baseline and ongoing echocardiogram monitoring during treatment and posttreatment have been implemented in the studies that have a >3-week treatment duration. To date, no clinically significant echocardiogram findings (only minor/trace or Grade 1 findings) have been observed.

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

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

3 OBJECTIVES AND ENDPOINTS

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

Table 3-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To investigate the effect of steady-state PSL (400mg BID or 200mg BID) on the PK of a single dose oral contraceptive containing EE 30µg and LN 150µg.	– C_{max} and AUC of EE and LN
Secondary	
• To evaluate the safety and tolerability of PSL in healthy female study participants.	– Incidence of TEAEs and SAEs
• To evaluate the effect of single-dose oral contraceptive containing EE 30µg and LN 150µg on the steady-state PK of PSL.	– $C_{max(ss)}$ and AUC_{τ} of PSL
Other	
• To evaluate the safety and tolerability of PSL in healthy female study participants.	– Changes in vital signs (oral or aural temperature, pulse rate, respiratory rate, and BP) – Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis) – Changes in 12-lead ECG assessments – Physical and neurological examination findings
• To evaluate the effect of a single-dose oral contraceptive containing EE 30µg and LN 150µg on the steady-state PK of PSL.	– CL_{ss}/F, C_{min}, t_{max}, $t_{1/2}$ of PSL

• To evaluate the effect of a single-dose oral contraceptive containing EE 30µg and LN 150µg on the steady-state PK of PSL metabolites	– AUC_{τ} and $C_{max,ss}$, t_{max}, $t_{1/2ss}$, C_{trough}, and metabolic ratios of AUC_{τ} and $C_{max,ss}$
• To investigate the effect of steady-state PSL on the PK of a single-dose oral contraceptive containing EE 30µg and LN 150µg	– T_{max}, $AUC_{(0-t)}$, $t_{1/2}$,and CL/F of EE and LN
• To collect and store blood samples for genotyping of drug metabolizing enzymes and/or transporters. (if needed)	– Potential genotyping of study participants for specific genes related to drug metabolizing enzymes and/or transporters.
• To collect venous plasma and blood samples (Mitra™) for cross-validation of PSL bioanalytical method	– Cross validation of PSL bioanalytical method.

BP=blood pressure; ECG=electrocardiogram; EE=ethinylestradiol; LN= levonorgestrel PK=pharmacokinetic; PSL=padsevonil; SAE=serious adverse event; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

This is a Phase 1, open label, randomized, two-way cross-over study to investigate the potential PK interaction of PSL with OC in healthy female study participants. The designs of Part 1 and Part 2 are shown in Table 1-2 and Table 1-3.

A study participant who provides written informed consent will be screened within 28 days before the first Treatment Period. Each Part of the study (Part 1 and Part 2) consists of a Screening Period, 2 Treatment Periods, a Washout Period, and a Safety-Follow-Up (SFU) Period of 7 to 10 days (Part 1) or 7 to 14 days (Part 2).

Study participants who meet all inclusion criteria and none of the exclusion criteria will check into the clinic the day prior to the first day of the first Treatment Period and will be randomized into one of the treatment sequences: Treatment Sequence A or Treatment Sequence B.

The Treatment Periods will consist of a single dose of OC or a dose of OC combined with multiple doses of PSL for a time period. The OC Treatment Periods are separated by a Washout Period lasting at least 14 days.

Part 1

Sequence A

In Part 1, study participants enrolled in Treatment Sequence A will be administered PSL BID (up-titration to steady-state [400mg BID]) from Day 1 to Day 5, followed by a steady-state period from Day 6 to Day 12 with a single dose of OC administered on the morning of Day 13. A taper of PSL will occur from Day 15 to Day 19. Starting on Day 20, the study participants will then complete a Washout Period for 14 days followed by a return to the clinic for the OC-only dosing on Day 34. Pharmacokinetic samples will be collected on the days shown in Table 1-2,

Treatment Sequence A. An SFU Visit will occur between Day 41 and Day 44. All assessments, including PK sampling, are shown in the Schedule of Activities (Part 1, Treatment Sequence A, Table 1-4).

Sequence B

Study participants enrolled in Treatment Sequence B will be administered a single dose of OC on the morning of Day 1 followed by PK assessments that day and the next 2 days. The study participants will then complete a 14-day Washout Period followed by a return to the clinic for the OC+PSL dosing from Day 18 to Day 36 (OC to be administered on Day 30). Pharmacokinetic samples will be collected on the days shown in Table 1-2, Treatment Sequence B. Study Participants will be administered PSL BID (up-titration to steady-state) from Day 18 to Day 22 followed by a maintenance period from Day 23 to Day 31. A taper of PSL will occur from Day 32 to Day 36. An SFU Visit will occur between Day 43 and Day 46. All assessments, including PK sampling, are shown in the Schedule of Activities (Part 1, Treatment Sequence B, Table 1-5.

Part 2

Sequence A

In Part 2, all study participants enrolled in Treatment Sequence A will be administered PSL 100mg BID on Day 1, with titration to 200mg BID for Day 2 to Day 8. A single dose of OC is administered on the morning of Day 9, at which time PSL is at steady-state. To taper, 100mg BID of PSL will be given on Day 11. Starting on Day 12, the study participants will then complete a Washout Period for 14 days followed by a return to the clinic for the OC-only Period on Day 25 (OC dosing on Day 26). Pharmacokinetic samples will be collected on the days shown in Table 1-3, Treatment Sequence A. An SFU Visit will occur between Day 33 and Day 40. All assessments, including PK sampling, are shown in the Schedule of Activities (Part 2, Treatment Sequence A, Table 1-6.

Sequence B

All study participants enrolled in Treatment Sequence B will be administered a single dose of OC on the morning of Day 1 followed by PK assessments that day and the next 2 days. The study participants will then complete a 14-day Washout Period followed by a return to the clinic for the OC+PSL dosing from Day 18 to Day 28 (OC to be administered on Day 26, at which time PSL is at steady state). Pharmacokinetic samples will be collected on the days shown in Table 1-3, Treatment Sequence B. Study participants will be administered PSL 100mg BID on Day 18, with titration to 200mg BID for Day 19 to Day 27. To taper, 100mg BID of PSL will be given on Day 28. An SFU Visit will occur between Day 35 and Day 42. All assessments, including PK sampling, are shown in the Schedule of Activities (Part 2, Treatment Sequence B, Table 1-7.

4.2 Scientific rationale for study design

The potential interaction between PSL and OC will be assessed with a two-way cross-over study design, which is deemed appropriate to reach the goal of the study.

In Part 1, PSL will be up-titrated from 100mg to 400mg BID over 5 days and, in Part 2, from 100mg BID to 200mg BID in 1 day to increase tolerability as demonstrated in previous clinical

pharmacology studies. Afterwards, a steady-state period of 7 days will take place before subjects receive OC. This 7-day steady-state period will ensure that the potential CYP3A4 induction (mediated by PSL) is close to its maximum level and will be appropriate to evaluate the effect on OC. After OC administration, PSL will be tapered.

The washout period between the 2 treatment periods has a duration of 14 days mainly to ensure that CYP3A4 enzyme activity is back to baseline.

Since the risk of DDI between OC and PSL is predicted to be low (PSL 400mg BID) or not clinically relevant (PSL 200mg BID) and to reduce the burden of continuous administration of PSL (over 2 menstrual cycles) at the MTD in healthy female study participants, the DDI potential of PSL will be assessed on a single dose of the chosen OC. Therefore, EE and LN PK parameters (C_{max} and AUC) will be used as primary endpoints and bioequivalence criteria will be applied for defining clinical relevance of the DDI ([redacted]). This PK-based approach has been used widely to assess DDI between OC and many drugs (Menon et al, 2016; Mohamed et al, 2018; Hurst et al, 2016; Crawford et al, 1990; Mildvan et al, 2002).

This study design will also allow evaluation of the effect of single dose OC on the steady-state PK of PSL and its metabolites.

Single dose OC is deemed appropriate to investigate the potential effect of EE/LN on PSL as there is no accumulation described with EE (Kuhnz et al, 1994). Though LN is known to accumulate (2 to 3-fold) following repeated administration (Kuhnz et al, 1994), there have been no CYP3A4/2C19 inhibition effects described in the literature (Palovaara et al, 2003); therefore, no DDI mediated by LN is expected.

4.3 Justification for dose

In Part 1, the rationale for the dose selected for this study is a balance between the desire to use the highest possible dose of PSL (as required by regulatory guidance) and the need to protect the safety and comfort of study participants. On this basis, the dose of 400mg BID (already identified as the MTD in earlier studies) was seen as the optimal dose for these purposes. A dose of 400mg BID is also potentially the highest dose currently planned for inclusion in the New Drug Application/Marketing Authorization Application (NDA/MAA).

However, although the CNS adverse events reported were similar to those seen in previous clinical trials with PSL, their overall impact has been more troublesome in some participants than in others receiving the same dose levels (PSL 400mg BID). Given that 14 study participants have already completed the study at 400mg BID (which will provide appropriate information on the DDI risk between OC and PSL at the highest anticipated dose to be included in the NDA/MAA), it seems appropriate to reduce the maximum dose administered in Part 2 to 200mg BID. As a consequence, treatment duration will be decreased from 19 days to 11 days (through reduction of the titration and taper period) and the total exposure of PSL (cumulative dose in mg) will be significantly reduced and will be similar to other ongoing clinical pharmacology studies. This is anticipated to reduce the AE burden on study participants but still permit adequate exploration of the potential DDI between PSL and OC at this dose, which is also potentially to be included in the NDA/MAA.

4.4 End of study definition

A study participant is considered to have completed the study if she has completed all periods of the study including the last scheduled procedure shown in the Schedules of Activities (Part 1, Treatment Sequence A, Table 1-4 and Treatment Sequence B, Table 1-5; Part 2, Treatment Sequence A, Table 1-6 and Treatment Sequence B, Table 1-7).

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

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 aged 18 years of age or greater, at the time of signing the informed consent.

Sex

2. Participant must be a premenopausal female with no indication of abnormal or gestational/lactational hypothalamic-pituitary-ovarian function. Menopause will be defined for the purpose of this study as amenorrhea of ≥12 months for which no other reason has been identified.

Type of participant and disease characteristics

3. Participant must not be pregnant (see Appendix 4; Section 10.4) or breastfeeding. Participant must agree to use an effective form of contraception (other than hormonal methods) for the duration of the Treatment Period and for at least 90 days (or 5 terminal half-lives) after the last dose of study medication.
4. Participant must be in good physical and mental health as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

Weight

5. Participant must have body weight of at least 45kg and body mass index within the range 18 to 30 kg/m^2 (inclusive).

Informed consent

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

5.2 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 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 exclusionary conditions will be determined based on the psychiatric history collected at Screening Visit.
2. Participant has a history of discontinued use of OC for medical reasons.
3. Participant has any medical reason that would contraindicate the administration of OC (per label).
4. Participant has used any of the following within the specified time period prior to first dose of study medication:
   a) OC or oral hormone replacement therapy within prior 30 days
   b) Implanted hormonal contraceptives within prior 6 months
   c) Injectable contraceptives within prior 12 months
   d) Topical controlled-delivery contraceptives within prior 3 months
   e) Hormone-releasing intrauterine devices ('coils') within prior 3 months.
5. Participant has other relevant gynecological disorders (such as premature ovarian failure or endometriosis).
6. Participant has a known hypersensitivity to any components of the study medication as stated in this protocol. Participant has sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.
7. Participant has abnormal BP according to the following:

   Participants must have blood pressure and pulse rate within normal range in the supine position after 5 minutes rest (SBP: 90mmHg to 145mmHg; DBP: 40mmHg to 95mmHg; PR: 40bpm to 100bpm) at Screening

   Any values marginally (ie, no more than 5mmHg) outside the normal range but considered not clinically significant by the Investigator are allowed. In the case of an out-of-range result, 1 repeat will be allowed. If the readings are out of range again, the study participant will not be included. On Day –1, if the results are deemed clinically significant by the principal investigator or designee, the study participant will not be included.
8. Participant has had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
9. Participant is unable to tolerate oral medication or has a history of gastric bypass surgery.

10. Participant has gastrointestinal disease with the potential to influence absorption, including motility disorders.
11. Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin, etc.) within 2 months prior to dosing. In case of uncertainty, the UCB Study Physician should be consulted.
12. Participant has a history of chronic alcohol or drug abuse within the previous 6 months. A pre-study drug/alcohol screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) is conducted to aid evaluation of this criterion. A participant with a positive finding on the drug screen may still be enrolled at the discretion of the Investigator if a plausible clinical explanation exists (eg, prior or concomitant medication use).
13. Participant has a history or presence of cardiovascular (eg, cardiac insufficiency, coronary heart disease, hypertension, arrhythmia, tachyarrhythmia, or myocardial infarction), respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study medication; or interfering with the interpretation of data.

Suicidality

14. 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 or "Since Last Visit" version at Baseline (Day -1).

Prior/concomitant therapy

15. Participant has received any prescription or nonprescription medicines, including enzyme inhibitors or inducers, over-the-counter (OTC) remedies, herbal and dietary supplements (including St. John's Wort), or vitamins up to 2 weeks or 5 half-lives of the respective drug (whichever is longer) before the first administration of study medication and during the clinical part of the study, unless required to treat an AE. This does not include medications listed in Section 6.5.1.

Prior/concurrent clinical study experience

16. Participant has participated in another study of a study medication within the previous 1 month (or 5 half-lives, whichever is longer) prior to Screening, or is currently participating in another study of a study medication, or has participated in >4 studies of a study medication within the past year or has previously been assigned to treatment in a study of the medication under investigation in this study.

Diagnostic assessments

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

18. Study participant has bilirubin >1.0xULN (isolated bilirubin <1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
19. Study participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
20. Participant has any clinically relevant ECG finding at the Screening Visit or at Baseline (Day -1) that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett's formula (QTcB) or Fridericia's formula (QTcF) >450ms in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval ≥220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out-of-range result, 1 repeat will be allowed. If the result is out-of-range again, the study participant cannot be included.

    NOTE A: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), or Fridericia's formula (QTcF). 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.
21. Participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
22. Participant tests positive for human immunodeficiency virus-1/2 antibody (human immunovirus-1/2Ab) at Screening or within 3 months prior to the first dose of study medication.
23. Participant tests positive for Hepatitis B surface antigen, or HCV-Ab at Screening or within 3 months prior to the first dose of study medication.

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

Other exclusions

24. Participant is, in the judgement of the Investigator, likely to be nonreliable or noncompliant or uncooperative during the study.
25. Participant has made a blood or plasma donation or has had a comparable blood loss (>450mL) within the last 30 days prior to Screening. Blood donation during the study is not permitted.
26. Participant has received blood or plasma derivatives within the 6 months preceding Screening.

27. 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).
28. 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.
29. Participant ingests grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before each administration of study medication. If this is the case at the start of the study, study participants may be rescreened.
30. Female participant tests positive for pregnancy, plans to get pregnant during participation in the study, or is breastfeeding.
31. Study participant has a diet that deviates notably from the "normal" amounts of protein, carbohydrate, and fat, as judged by the Investigator.
32. Study participant has undergone sudden and/or extreme changes in exercise levels for 2 weeks prior to Screening Visit.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Study participants will complete a light meal 30 minutes prior to each morning dose of PSL and will complete a standard meal 30 minutes prior to the evening dose. The standardized meal composition and timing should be consistent for all days the participant is on study. On days when PK assessments will be taken, study participants will complete a standardized meal (same macronutrients will be administered for minimizing covariates) in the afternoon and evening.
- Padsevonil will be administered orally with 8oz (240mL) water. Between 1h predose and 2h postdose, the total intake of beverages should be limited to 100mL. On PK sampling days, study participants must be dosed in an upright position and must remain semi-recumbent until 4 hours after the morning dose of PSL (apart from when required to do otherwise for study assessments such as vital signs, ECGs, etc).
- The study participant must not ingest grapefruit, starfruit, and pawpaw (as beverage, fruit, or supplements) within 72h before the study medication administration. These fruits are not allowed during the Treatment Period and throughout the study.

5.3.2 Caffeine, alcohol, and tobacco

- During 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 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 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

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

5.4 Screen failures

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

5.4.1 Rescreening

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Study participants may be rescreened under conditions such as the following:

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

Study participants may be included if the repeat values for the laboratory screening criteria are within normal ranges and/or if repeat values show normalization of the out-of-range safety laboratory values, and/or after the study participant makes a complete recovery from the mild or moderate illness, and if all other screening criteria are met.

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

Rescreened study participants will be assigned a new participant number.

6 STUDY TREATMENTS

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

6.1 Treatments administered

A summary of the study treatments administered is provided in Table 6-1. Treatments will be administered in an open-label fashion and study participants will be dosed in an upright position. On PK sampling days, study participants must remain semi-recumbent until 4 hours after the morning dose of PSL (apart from when required to do otherwise for study assessments such as vital signs, ECGs, etc).

Table 6-1: Study medications administered

Study Medication Name:	Padsevonil
Dosage formulation:	Tablets
Unit dose strength(s)/Dosage level(s)**:**	100mg tablets for BID dosing
Route of Administration:	Oral
Dosing instructions:	All treatments will be administered orally with 8oz (240mL) water. The use of beverages between 1h predose and 2h postdose should be limited to a maximum of 100mL (in order to keep groups comparable with respect to period of dosing). Study participants will complete a light meal 30 minutes prior to each morning dose of PSL and will complete a standard meal 30 minutes prior to the evening dose of PSL. Treatments will be administered in an open-label fashion. Study participants will be dosed in an upright position. On PK sampling days, study participants must remain semi-recumbent until 4 hours after the morning dose of PSL (apart from when required to do otherwise for study assessments such as vital signs, ECGs, etc).
Packaging and Labeling	Padsevonil tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws and regulations.
Manufacturer	UCB

Study Medication Name:	Single dose Microgynon 30® (ethinyl estradiol 30µg+levonorgestrel 150µg)
Dosage formulation:	Tablets
Unit dose strength(s):	(ethinyl estradiol 30µg+levonorgestrel 150µg)
Route of Administration:	Oral
Dosing instructions:	Dosing instructions are provided in the UP0035 IMP Handling Manual (IMP Instructions for Handling).
Packaging and Labeling	Tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws and regulations
Manufacturer	Bayer

IMP=investigational medicinal product; PSL=padsevonil

6.2 Preparation, handling, storage, and accountability requirements

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

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

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

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the UP0035 IMP Handling Manual.

Further guidance and information for the final disposition of unused study medication are provided in the UP0035 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-study participant basis and will serve as source documentation during the course of the study. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the study medication is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: randomization and blinding

This study is an open-label study; therefore, no study personnel or study participants will be blinded.

A contract research organization (CRO; ie, ICON) randomization biostatistician will create the program to generate the randomization code. A dummy randomization schedule will be prepared by the randomization biostatistician (a cross-over 2x2 scheme with 2 treatment sequences) 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 and will be

reviewed by a quality control randomization biostatistician. 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 staff for SAE reporting
- Bioanalytical staff (to identify samples to be measured)
- A member of pharmacy involved in IMP preparation and dispensing
- The Clinical Study Biostatistician/Statistical Programmer

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

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

Each study participant will receive a 5-digit study participant number, from a range of numbers supplied by UCB Clinical Data Operations, Technology, and Standards, assigned at Screening that will serve as the study participant identifier throughout the study. The study participant number will be required in all communication between the Investigator/designee.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study medication blind

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

6.3.1.2 Breaking the study medication blind in an emergency situation

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

6.4 Treatment compliance

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

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The use of concomitant medications during this study should be avoided unless necessary to treat AEs or unless approved on a case-by-case basis prior to enrollment. The use of any concomitant

medications should be approved by the Sponsor in advance, in writing, when possible. The following concomitant medications are permitted during the study:

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

6.5.2 Prohibited concomitant treatments (medications and therapies)

With the exception of permitted concomitant treatments listed in Section 6.5.1, prescription or nonprescription medicines, including OTC remedies and herbal and dietary supplements (including St John's Wort), are prohibited within 14 days or 5 half-lives (whichever is longer) before administration of PSL and during the Treatment Period, unless required to treat an AE. Drugs of unknown half-life are prohibited within 14 days before administration of PSL and during the Treatment Period, unless required to treat an AE. The use of any inducers or inhibitors of CYP2C19 or CYP3A4 is prohibited.

Combined (estrogen and progestogen containing) hormonal contraception and progesterone only hormonal contraceptive methods are not permitted in this study (Section 10.4).

6.5.3 Rescue medication

Not applicable.

6.6 Dose modification

No PSL dose modifications are permitted during the study for an individual study participant.

6.7 Treatment after the end of the study

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

7 DISCONTINUATION OF STUDY MEDICATION AND STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

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

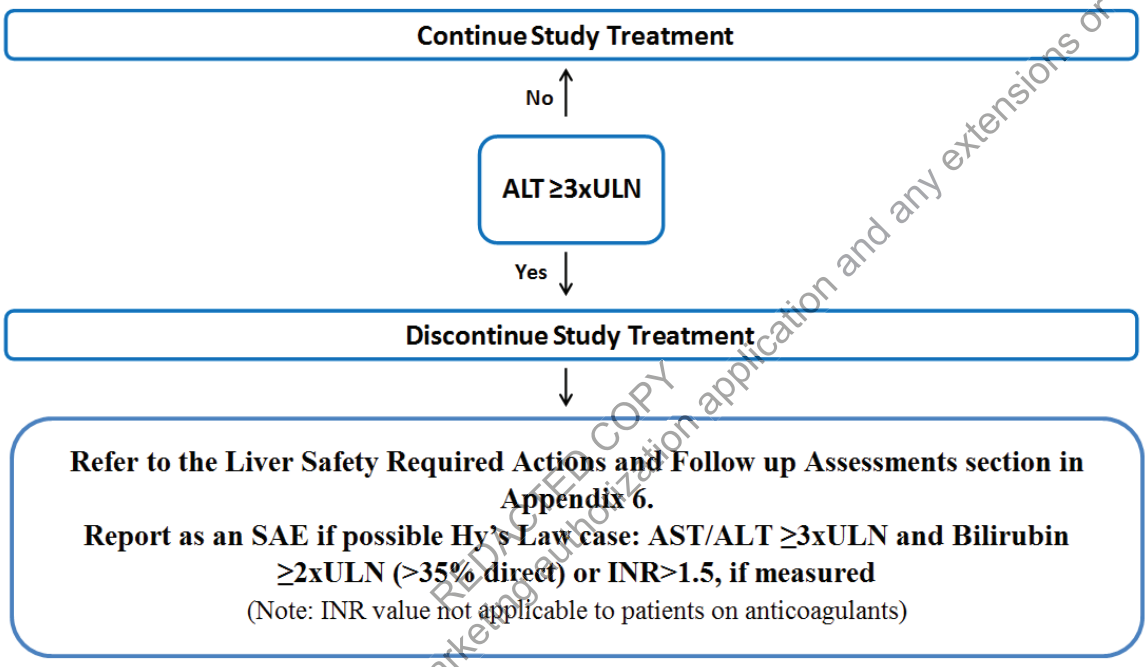
In all cases the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB Study Physician. Study participants withdrawn from the study should complete PSL tapering. Investigators should contact the UCB Study Physician, in advance whenever possible, to discuss the withdrawal of a study participant and the appropriate schedule of tapering under the circumstances. No restart will be allowed.

7.1.1 Liver chemistry stopping criteria

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

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

Figure 7-1: Liver chemistry stopping algorithm



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

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

7.1.2 QTc stopping criteria

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

- QTc ≥500msec
- Change from baseline: QTc ≥60msec

If a clinically significant finding is identified (including, but not limited to, changes from Baseline in QTcB or QTcF after enrollment), the Investigator or qualified designee will determine if the study participant can continue in the study and if any change in study participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the Schedules of Activities (Part 1, Treatment Sequence A, Table 1-4 and Treatment Sequence B, Table 1-5; Part 2, Treatment Sequence A, Table 1-6 and Treatment Sequence B, Table 1-7) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Criteria for study hold due to adverse events

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

- 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 a single part of the study (Part 1 or Part 2), independent of within or not within the same SOC.

If either stopping criterion is met, the trial will be put on temporary halt. However, tapering of PSL doses, and completion of the OC-only treatment period in Sequence A will be allowed. 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 10.3).

7.3 Study 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 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, she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Upon early termination/withdrawal, the study participant will be administered tapering doses of the study medication and will complete SFU Visit assessments following the last dose of study medication. In all cases, such withdrawals and the degree of tapering should be discussed first with the UCB Study Physician, wherever possible.

See the Schedules of Activities (Part 1, Treatment Sequence A, Table 1-4 and Treatment Sequence B, Table 1-5; Part 2, Treatment Sequence A, Table 1-6 and Treatment Sequence B, Table 1-7) 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 her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requests withdrawal of the study participant.
7. Study participant has changes in the ECG results that are regarded as clinically significant and/or that worsen over time.
8. Study participant has an ECG that shows an absolute value for QTcB or QTcF ≥500ms or ≥60ms above Baseline.
9. Study participant develops a second- or third-degree atrioventricular block or another clinically relevant change in ECG results as determined by the Investigator.
10. Study participant has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The study participant should be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgement of the benefit/risk of continuing the study participant in the study on PSL.
11. Study participant has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The study participant should be referred immediately to a mental healthcare professional and must be withdrawn from the study.

12. Study participant is suspected of having a serious multiorgan hypersensitivity reaction. Serious suspected multiorgan hypersensitivity cases may be identified and reported to the Sponsor by the Investigator using the following algorithm:
    - An AE or laboratory value (as defined below) suggestive of internal organ involvement including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.
    - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
        - Eosinophils percentage ≥10%
        - Eosinophils absolute ≥0.5G/L
        - Neutrophils absolute <1.5G/L
        - Platelets absolute ≤100G/L

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

Study participants withdrawn from the study should complete the Taper Period described in the PSL+OC portion of the study. Investigators should contact the UCB Study Physician, whenever possible, to discuss the withdrawal of a study participant in advance.

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

7.4 Lost to follow-up

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

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

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

Should the study participant continue to be unreachable, 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 Schedules of Activities (Part 1, Treatment Sequence A, Table 1-4 and Treatment Sequence B, Table 1-5; Part 2, Treatment Sequence A, Table 1-6 and Treatment Sequence B, Table 1-7). 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 study participant should continue or discontinue study medication.

Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.

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

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

8.1 Pharmacokinetics

Whole blood will be collected for measurement of plasma concentrations of PSL as specified in the Schedule of Activities. 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 and each dose of OC or PSL administered will be recorded. Plasma samples will be collected for measurement of plasma concentrations and to evaluate the PK of PSL, EE, and LN as specified in the appropriate Schedule of Activities.

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

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

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

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

Table 8–1: Irrelevant time deviations for PK sampling

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

PK=pharmacokinetic

8.1.1 Mitra™

As described in Schedule of Activities, Mitra™ samples will be collected for cross-validation of PSL bioanalytical method. These additional samples will be taken on a limited number of study participants (ideally, at least 9 from each study part) who will agree and consent for the additional blood sampling for this study objective. However, a lower number of study participants may be allowed at the discretion of the principal investigator and sponsor.

8.2 Pharmacodynamics

Not applicable.

8.3 Safety assessments

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

8.3.1 Physical examination

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

A brief physical examination will be conducted only as needed. A brief physical examination will include, at a minimum, assessments of general appearance, skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.3.2 Vital signs

Oral or aural temperature, PR, RR, and BP will be assessed. Whichever method of temperature measurement is used should be used for all evaluations for that study participant, and ideally across all study participants.

Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

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

8.3.3 Electrocardiograms

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

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

Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.3.4 Clinical safety laboratory assessments

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

The Investigator must review the laboratory reports, document these reviews, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are laboratory findings that changed considerably or that increased in frequency or intensity more than expected as compared with the clinical profile known to the Investigator from the study participant's history or Screening Visit.

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 UCB Study Physician notified.

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

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered

clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.3.5 Suicidal risk monitoring

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

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All study participants will complete the "Screening/Baseline" version of the C-SSRS during Screening (assessing the past 6 months), followed by the "Since Last Visit" version at the visits indicated on the Schedule of Activities.

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

8.3.6 Psychiatric and Mental Status

The psychiatric and mental status of study participants will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. The Psychiatric and Mental Status assessment will be performed according to the Schedule of Activities. The parameters that will be evaluated cover orientation, attention, memory, mood, calculus, behavior, and thinking or feeling. These parameters will be assessed as normal or abnormal and then determined whether clinically significant. If present and abnormal, psychiatric symptoms, mental impairment, and behavioral problems will be assessed as to whether they are clinically significant.

8.4 Adverse events

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

Adverse events will be reported by the study participant.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the study participant to discontinue PSL or UP0035 (see Section 7).

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF and at the time points specified in the Schedule of Activities.

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

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

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

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

8.4.2 Method of detecting AEs and SAEs

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

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.4.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.4.4 Regulatory reporting requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

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

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

8.4.5 Pregnancy

Details of all pregnancies will be collected after the start of study medication and until up to 30 days after the birth for any significant medical issues. In certain circumstances, UCB may request that follow-up is continued for a period up to 12 months. If the study participant is lost to follow-up and/or refuses to give information, written documentation of attempts to contact the study participant 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 the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 Section 10.4).

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

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

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

8.4.6 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. No AEs of special interest have been identified for PSL to date, with the exception of potential Hy's Law as described below.

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

8.5 Safety signal detection

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

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.

8.6 Efficacy assessments

Not applicable.

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/or symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

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

In the event of an overdose, the Investigator should:

1. Contact the UCB Study Physician immediately.
2. Closely monitor the study 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 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

Archived blood samples for genotyping of drug metabolizing enzymes and/or transporters will be collected as specified in the Schedule of Activities.

8.9 Biomarkers

Not applicable.

8.10 Samples for PSL bioanalytical method cross-validation

Mitra™ and venous blood samples will be collected as specified in the Schedule of Activities. The bioanalytical results from these samples will not be reported in the clinical study report. They will be included in the bioanalytical cross validation report.

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.

- Safety Set (SS): All study participants who received at least one dose of study medication.
- Pharmacokinetic Per Protocol Set (PK-PPS): the PK-PPS is a subset of the SS, consisting of those study participants who had no important protocol deviations affecting the PK of EE, LN, or PSL and its metabolites and for whom at least one measurable concentration exists.

9.2 General statistical considerations

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

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

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

9.3 Planned pharmacokinetic analyses

All PK analyses will be performed using the PK-PPS. Pharmacokinetic parameters of EE, LN, PSL, and PSL metabolites (eg, C_{max}, t_{max}, AUC or AUC_{0-t} or AUCτ, $t_{1/2}$ or CL/F) will be estimated using noncompartmental analysis with Pharsight Phoenix® WinNonlin® v6.3 (or higher) software. Pharmacokinetic analyses will be performed and reported for each study part (Part 1 and Part 2).

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

Ethinylestradiol/levonorgestrel primary PK parameters will be compared between treatments using analysis of variance for a cross-over design (treatment, period, sequence as fixed effects, and subject within sequence as random effect) on the log-transformed parameters and estimation of the geometric mean ratio of PK parameters between groups with their 90% CI will be provided.

Lack of PSL effect on EE/LN will be concluded if the 90% CI of the geometric mean ratio between treatment PSL+EE/LN and treatment EE/LN of the least squares means for the log-transformed AUC, and C_{max} is within the bioequivalence acceptance range of 80% to 125%.

If the 90% CI is slightly broader than the BE criteria, individual AUC and Cmax geometric means ratios will be assessed with the aim of achieving >0.7 (less than a 30% decrease OC exposure in the presence of PSL) to declare a lack of a clinically significant PK interaction.

Pharmacokinetic parameters ($C_{max,ss}$, AUC_{τ}) of PSL and its metabolites will be compared between days with OC [Part 1: Day 13 for Treatment Sequence A and Day 30 for Treatment

Sequence B; Part 2: Day 9 for Treatment Sequence A and Day 26 for Treatment Sequence B] and without OC [Part 1: Day 12 for Treatment Sequence A and Day 29 for Treatment Sequence B; Part 2: Day 8 for Treatment Sequence A and Day 25 for Treatment Sequence B] using analysis of variance on the log-transformed parameters and estimation of geometric ratio of PK parameters between days with their 90% CI will be provided.

The relationship between individual AUC ratio (with and without PSL) of EE and LN, and the exposure to PSL (AUCτ) will be assessed by scatterplots and linear regression analyses (log-transformed and also untransformed data).

The estimated slope with 95% CI will be computed. In absence of interaction, intercept and slope will be equal to 0.

9.4 Planned safety analyses

All safety analyses will be performed using the SS. All safety variables will be listed and summarized by study part and treatment (OC with PSL, OC alone, and PSL alone when applicable) and time point, when applicable.

All AEs will be coded using the Medical Dictionary for Regulatory Activities and characterized as pretreatment and treatment-emergent according to the intake of the study medications (PSL, OC). 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 AEs will be summarized by treatment according to the intake of PSL (pretreatment or treatment-emergent) and by intensity or relationship to PSL.
- Safety laboratory measurements, vital signs, and 12-lead ECGs parameters will be tabulated using descriptive statistics. Laboratory values outside the reference range will be flagged in the listings. Any PDILI events will be listed.
- Assessment of suicidality will be listed.
- Physical and neurological examinations abnormalities will be listed.

9.5 Planned efficacy/outcome analyses

Efficacy is not being evaluated in this study.

9.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant. Furthermore, study participants will be excluded from the SS 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 process prior to database lock to confirm exclusion from analysis sets.

9.7 Handling of dropouts or missing data

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

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

9.8 Planned interim analysis and data monitoring

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

9.9 Determination of sample size

Lack of PK interaction in this study will be concluded if 90% confidence intervals for both AUC and C_{max} geometric means ratios (with/without PSL) of LN and EE are included in the 80% to 125% bioequivalence range.

In a previous OC interaction study conducted by UCB with brivaracetam (N01282), an intra-subject coefficient of variation of 10% for AUCt for both EE and LN (including C_{max}) and 16% for C_{max} was observed for EE.

Provided that the ratio of the expected means for test (with PSL) and reference (without PSL) is included in the range [0.90, 1.10] and for a type-I error of 0.05 and an intra-subject coefficient of variation of 16%, a total sample size of 34 study participants should allow at least 90% power for the assessment of lack of interaction (or 26 study participants for 80% power).

A total of 40 study participants will be randomized: Part 1 (PSL 400mg BID) will include 14 study participants and will allow a good estimate of the different ratios of PK parameters. Part 2 (PSL 200mg BID) will include 26 study participants (13 study participants in each sequence). Assuming no drop-outs, a decrease of 10% in PK parameters of OC and intrasubject coefficient of variation of 16%, this will allow 80% power for assessing lack of PK interaction.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

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

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

Prior to participation in the study, the ICF should be signed and personally dated by the study participant, or her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The study participant or 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 her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

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

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

10.1.4 Data protection

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

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, and 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 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 her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, or by inspectors from regulatory authorities.

10.1.5 Committees structure

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

10.1.6 Data quality assurance

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

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

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

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

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

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

10.1.6.1 Case Report form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.6.2 Apps

Not applicable.

10.1.7 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

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

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

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

10.1.8 Study and site closure

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

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

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

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

10.1.9 Publication policy

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

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

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

10.2 Appendix 2: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocyte count	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis[b]	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick. If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.			
Other Screening Tests	• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Alcohol breath test • Pregnancy test: Serum human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential) • Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab, syphilis; hepatitis E RNA) The results of each test must be entered into the eCRF.			

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

[b] Serum pregnancy testing (not urine) will be standard for this protocol.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement 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 condition detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Important medical events

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

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

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

AE and SAE Recording

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the participant is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

Reporting of SAEs

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

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

10.4.1.1 Woman of childbearing potential

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

In this study, the only women considered to be of non-childbearing potential who are eligible for inclusion are:

1. Premenopausal females with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.4.2 Contraception guidance

10.4.2.1 Male participants

Not applicable.

10.4.2.2 Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Serum beta human chorionic gonadotropin (HCG) pregnancy testing will be performed at all timepoints mentioned in the Schedule of activities.
- The result must be negative prior to dosing the study participant.

10.4.2.3 Collection of pregnancy information

10.4.2.3.1 Female participants

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

Table 10-1: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen and progestogen containing) hormonal contraception and progesterone only hormonal contraceptive methods are **not** permitted in this study.
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

10.4.2.3.2 Male participants with partners who become pregnant

Not applicable.

10.4.2.3.3 Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 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 8.4.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Genetics

Genetics are not evaluated in this study; however, a blood sample will be taken for potential genotyping of metabolizing enzymes and/or drug transporters. Genotyping samples will be destroyed once the clinical study report has been finalized, approximately 1 year after the end of the study.

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

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

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

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

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

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

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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT≥3xULN If ALT ≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin) OR international normalized ratio (INR) >1.5, report as a serious adverse event (SAE).[a,b] See additional actions and follow-up assessments listed below.
Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**

• Report the event to the UCB **within 24 hours.** • Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Viral hepatitis serology.[c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury or hypersensitivity on the AE eCRF. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF. **<u>If</u> ALT ≥3xULN AND <u>bilirubin</u> ≥2xULN <u>or INR</u> >1.5<u>:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (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.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick, which is indicative of direct bilirubin elevations suggesting liver injury.

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

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

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

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BID	twice per day
BP	blood pressure
cBZR	central benzodiazepine receptor
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic Case Report form
EE	ethinylestradiol
ES	enrolled set
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HCV-Ab	hepatitis C antibody
HIV	human immunovirus
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IMP	investigational medicinal product
IRB	Institutional Review Board
LEV	levetiracetam
LFT	liver function test
LN	levonorgestrel
MTD	maximum tolerated dose
NDA	New Drug Application
OC	oral contraceptive
OTC	over-the-counter
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PR	pulse rate
PS	Patient Safety
PSL	Padsevonil
QTc	QT interval corrected
QTcB	QT interval corrected for Bazett's formula
QTcF	QT interval corrected for Fridericia's formula
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-up
SS	safety set
SV2	synaptic vesicle protein 2
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	women of childbearing potential

10.11 Appendix 11: Protocol Amendment History

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

Amendment 1: 10 Oct 2019

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol has been amended to comply with changes requested by 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). Changes were made in Section 7.2 (Criteria for study hold due to adverse events) to comply with MHRA requirement to align with European Medicines Agency Guidance on risk mitigation in first-in-human and early clinical trials, and to add an additional electrocardiogram (ECG) measurement at Day 14 (for Treatment Sequence A) and Day 31 (for Treatment Sequence B).

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Treatment Sequences	Day of oral contraceptive administration was changed from Day 31 to Day 30 in Treatment Sequence B to align with the rest of the protocol.	Correction
Section 1.3 Schedule of activities	An additional ECG measurement at Day 14 (for Treatment Sequence A) and Day 31 (for Treatment Sequence B) were added to the schedule of activities.	Add an additional ECG assessment
Section 1.3 Schedule of activities	Physical exam and blood sampling for cross-validation in Treatment Sequence B have been changed from Day 30 to Days 23 to 29 to align with the assessment days described in Treatment Sequence A.	Correction to align schedule of activities between Treatment Sequence A and Treatment Sequence B.
Section 1.3 Schedule of activities	Administer OC and blood sampling for OC PK level were changed from Day 31 to Day 30. Footnotes g, h, and i were updated to correct the days blood samples are to be collected.	Correction to align schedule of activities between Treatment Sequence A and Treatment Sequence B.
Section 5.2-Exclusion Criteria	Language specifying an adult cohort in exclusion criterion #7 has been removed for clarification purposes, as all participants in this study are adults. Changed exclusion criterion #18 to include that isolated bilirubin must be <1.5xULN instead of >1xULN. The	Update exclusion criteria

Section # and Name	Description of Change	Brief Rationale
	exception of asymptomatic gallstones was removed from exclusion criterion #19.	
Section 5.2-Exclusion Criteria	Exclusion criterion #19 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 7.2 Criteria for study hold due to adverse events	The criteria have been amended to align with the EMA Guidance on risk mitigation in first-in-human and early clinical trials.	Regulatory alignment
Section 10.5 Appendix 5: Genetics	The language describing sample collection was updated for clarity.	Language clarification
Section 10.4.2.3.1 Female participants	Brand names of IUDs containing hormones were removed.	Correction

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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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