A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, SINGLE-CENTER, CROSS-OVER STUDY TO INVESTIGATE THE PHARMACODYNAMIC, PHARMACOKINETIC, SAFETY, AND TOLERABILITY PROFILES OF PADSEVONIL IN HEALTHY STUDY PARTICIPANTS RECEIVING EITHER ETHANOL OR CANNABIDIOL

PROTOCOL UP0071 AMENDMENT 1

PHASE 1

Short title:

A pharmacodynamic, pharmacokinetic, safety, and tolerability study of padsevonil in healthy study participants receiving either ethanol or cannabidiol.

Sponsor:
UCB Biopharma SPRL
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1070 Brussels
BELGIUM

Regulatory agency identifying number(s):

Eudra CT Number:	2019-000703-32

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment1	25 Jul 2019	Substantial
Original Protocol	13 May 2019	Not applicable

Amendment 1 (25 Jul 2019)

Overall Rationale for the Amendment

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

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

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

Section # and Name	Description of Change	Brief Rationale
Section 1.1.4, Objectives and endpoints	Added smooth pursuit as a secondary objective	This was inadvertently omitted from the original protocol.
Section 1.3, Schedule of activities, Table 1-3	Footnote a was clarified.	Need to collect sample for clinical laboratory tests early enough for results to be available prior to dosing.
Table 1-5	Footnote o was clarified.	Need for predose CBD PK sample.
Table 1-7	Hem/chem/urine moved from D1 ato D-1.	Need to collect sample for clinical laboratory tests early enough for results to be available prior to dosing.
Table 1-9	Removed Hem/chem/urine from Day 1	Safety lab were mistakenly duplicated in the Schedules of Assessments.
Section 3, Objectives and endpoints, Table 3-1	Added smooth pursuit as a secondary objective	This was inadvertently omitted from the original protocol.
Section 7.1.3	Revised the study hold criteria	See overall rationale for the amendment.

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 (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

1.1.1 Protocol title:

A double-blind, placebo-controlled, randomized, single-center, cross-over study to investigate the pharmacodynamic (PD), pharmacokinetic (PK), safety, and tolerability profiles of padsevonil (PSL) in healthy study participants receiving either ethanol or cannabidiol (CBD).

1.1.2 Short title:

A PD, PK, safety, and tolerability study of PSL in healthy study participants receiving either ethanol or CBD.

1.1.3 Rationale:

This study aims to characterize the PD, PK, safety, and tolerability of steady-state PSL in healthy study participants receiving either ethanol or steady-state treatment of CBD. Drug-drug interactions that result in alterations in the PK of antiepileptic drugs (AEDs) can have a profound impact on tolerability, efficacy, and safety, and can potentially result in toxicity. It is therefore important to consider and estimate at an early stage the possible interactions that may occur with the concomitant use of PSL and other drugs.

1.1.4 Objectives and endpoints

Objectives	Endpoints
Primary	
• Part A: To evaluate the PD interaction between steady-state treatment with PSL and ethanol	• Smooth pursuit (%) to assess eye movement coordination and attention
• Part B: To evaluate the PK interaction between steady-state treatment with PSL and CBD	• $C_{max,ss}$ and AUC_{τ} obtained from the plasma concentration-time profiles for PSL and CBD
Secondary	
• Part A: To evaluate the PK interaction between steady-state treatment with PSL and ethanol	• Ethanol dose infused over time • $C_{max,ss}$ and AUC_{τ} obtained from the plasma concentration-time profiles for PSL
• Part B: To evaluate the PK interaction between steady-state treatment with PSL and CBD	• $t_{1/2}$, and $CL_{ss/F}$ obtained from the plasma concentration-time profiles for PSL and CBD
• Parts A and B: To evaluate the PD interaction between steady-state treatment with PSL and ethanol or between steady-state treatment with PSL and CBD	• Smooth pursuit (%) to assess eye movement coordination and attention (Part B only)

	• Saccadic peak velocity (degrees/sec) to assess sedation • Adaptive tracking (%) to assess visuo-motor control and vigilance • Body Sway to assess postural stability
• Parts A and B: To evaluate the safety and tolerability of PSL in study participants receiving concomitant ethanol or CBD	• Adverse events (AEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation of the study
Other	
• Parts A and B: To evaluate the safety and tolerability of PSL in study participants receiving concomitant ethanol or CBD	• Vital signs (pulse rate, respiratory rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) • 12-lead electrocardiogram (ECG) parameters • Physical examination findings • Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)
• Parts A and B: To evaluate the PD interaction between steady-state treatment with PSL and ethanol or steady-state treatment with PSL and CBD	• Visual analogue scales (VAS) Bond & Lader to assess study participantive alertness, mood, and calmness • VAS feeling high, internal and external perception (Bowdle) • VAS for alcohol intoxication to assess study participantive effects of ethanol (Part A only)
• Part B: To evaluate the PK interaction between steady-state treatment with PSL and CBD	• t_{max} obtained from the plasma concentration-time profiles for PSL and CBD • $C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,}$ and metabolite/parent (based on $C_{max,ss}$ and AUC_{τ}) obtained from the plasma concentration-time profiles for PSL metabolites and CBD active metabolite
• Part A and B: To collect and store blood for potential ADME genotype (if needed)	• Possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL (and metabolite) PK analyses, if needed

• Part A and B: To collect urine samples for additional PK analyses depending on the outcome of PSL (and metabolite) PK analyses, if needed	• Urine sample PK analysis

1.1.5 Overall design

This is a Phase 1, double-blind, randomized, placebo-controlled, single-center, cross-over study to evaluate the PK, PD, safety, and tolerability of steady state treatment of PSL in healthy study participants receiving either ethanol (Part A) or steady-state treatment of CBD (Part B). Study participants that complete Part A of the study are not eligible to complete Part B; similarly, study participants that complete Part B are not eligible to complete Part A.

1.1.5.1 Part A

Treatment Periods 1 and 2, and 4 and 5 are 2-way cross-over, placebo-controlled, ethanol-clamping periods with a washout of at least 2 days between Treatment Periods 2 and 3; PSL is not administered in Treatment Periods 1 and 2. Treatment Period 3 is an open-label PSL up-titration period toward a maintenance level of 200mg BID, and is immediately followed by Treatment Period 4 and Treatment Period 5. Treatment Period 6 is the PSL tapering open-label period.

During each cross-over period, the study participant will check into the clinic the evening prior to the day of administration of ethanol/dummy infusion and PSL (Day -1). On Day 1 of Treatment Periods 1, 2, 4 and 5, continuous infusion of ethanol or dummy infusion will begin with a 30 minute loading phase and will continue for 5 hours. On Day 1 of Treatment Periods 4 and 5, PSL will be administered right after the end of the loading phase.

During the first 10 minutes, the infusion will be accompanied by an infusion of 5% glucose via the same line in order to mask the sensation at the beginning of the ethanol infusion. The ethanol infusion rate is initially based on weight, height, age, and sex. The infusion rate is determined based on the Watson estimate of body water (Watson et al, 1980). Subsequently, the infusion rate will be adjusted based on breath ethanol measurements to maintain breath ethanol levels (and by extension, blood ethanol levels) of 0.6g/L. Following administration of PSL, the study participant will be observed for approximately 24 hours.

1.1.5.2 Part B

Treatment Period 1 of Part B will be conducted in a sentinel cohort of healthy study participants in order to evaluate CBD safety and PK exposure under a single dose of CBD 10mg/kg (fasted conditions). The results of the PK analysis will be compared to published PK data of CBD (dose of 750mg in fasted conditions) obtained in similar conditions with Epidiolex® (Taylor et al, 2018). The decision to continue on with the rest of Part B or terminate the study following the first CBD dose in Treatment Period 1 of Part B will be made pending the outcome of the analysis of CBD safety and exposure. A difference between the PK results in the present study and the literature findings requiring a >2-fold dose adjustment will be considered as not manageable and would result in termination of the study. If a dose adjustement ≤2-fold is needed, then the study will proceed with the second dose of CBD of Treatment Period 1 in Part B. If the observed CBD exposure matches the data from the literature, then study will proceed directly to Treatment

Period 2 of Part B (no second dosing of CBD will be required). Treatment Period 2 cannot commence until the results from Treatment Period 1 are analyzed.

A washout of at least 6 days will occur between Treatment Period 1 and Treatment Period 2. Treatment Period 2 will include 7 days of treatment with open-label PSL treatment. Treatment Period 3 starts after a washout of minimally 6 days for all study participants, and includes an ambulatory open-label CBD up titration of 16 days toward a maintenance level of 10mg/kg BID.

Treatment Periods 4 and 5 are 2-way cross-over, double-blind and placebo-controlled periods with PSL up titrated to a maintenance level of 200mg BID through Day 5 and subsequent down titration until Day 8. A maintenance dose of 10mg/kg BID CBD will occur in-house between Treatment Periods 4 and 5. Cannabidiol down titration starts in Treatment Period 6.

1.1.6 Number of participants

Based on the study PK and PD objectives, the total planned number of healthy study participants will be 44, including 22 evaluable participants for Part A and 22 evaluable participants for Part B. Drop outs will be replaced at the discretion of the Investigator and Sponsor. A total of 16 evaluable study participants are needed to complete Treatment Period 1 of Part B.

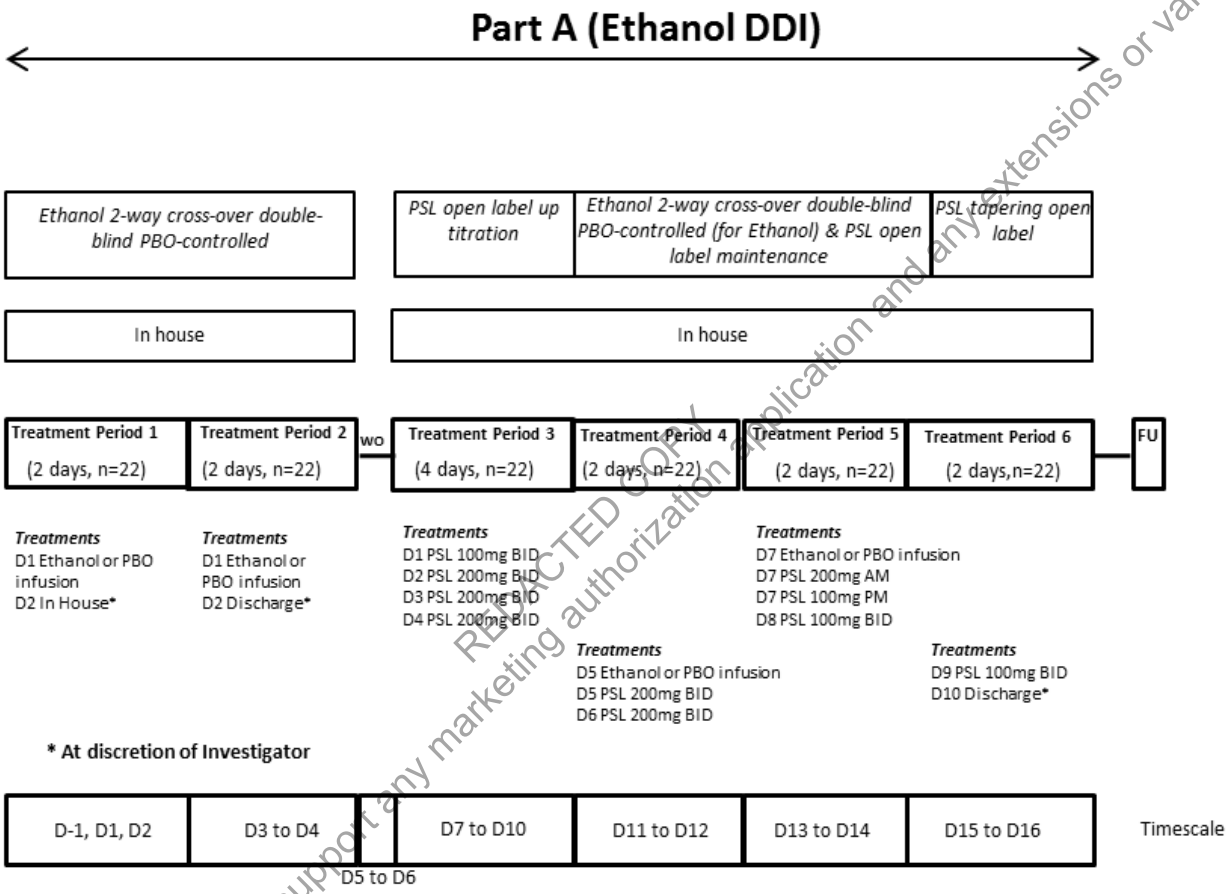
1.1.7 Treatment groups and duration

The maximum total duration is 54 days for Part A and 116 days for Part B (including Screening, the Treatment Period, and Follow-up) for each participant. The total duration of PSL exposure is 10 days in Part A and 21 days in Part B.

1.2 Schema

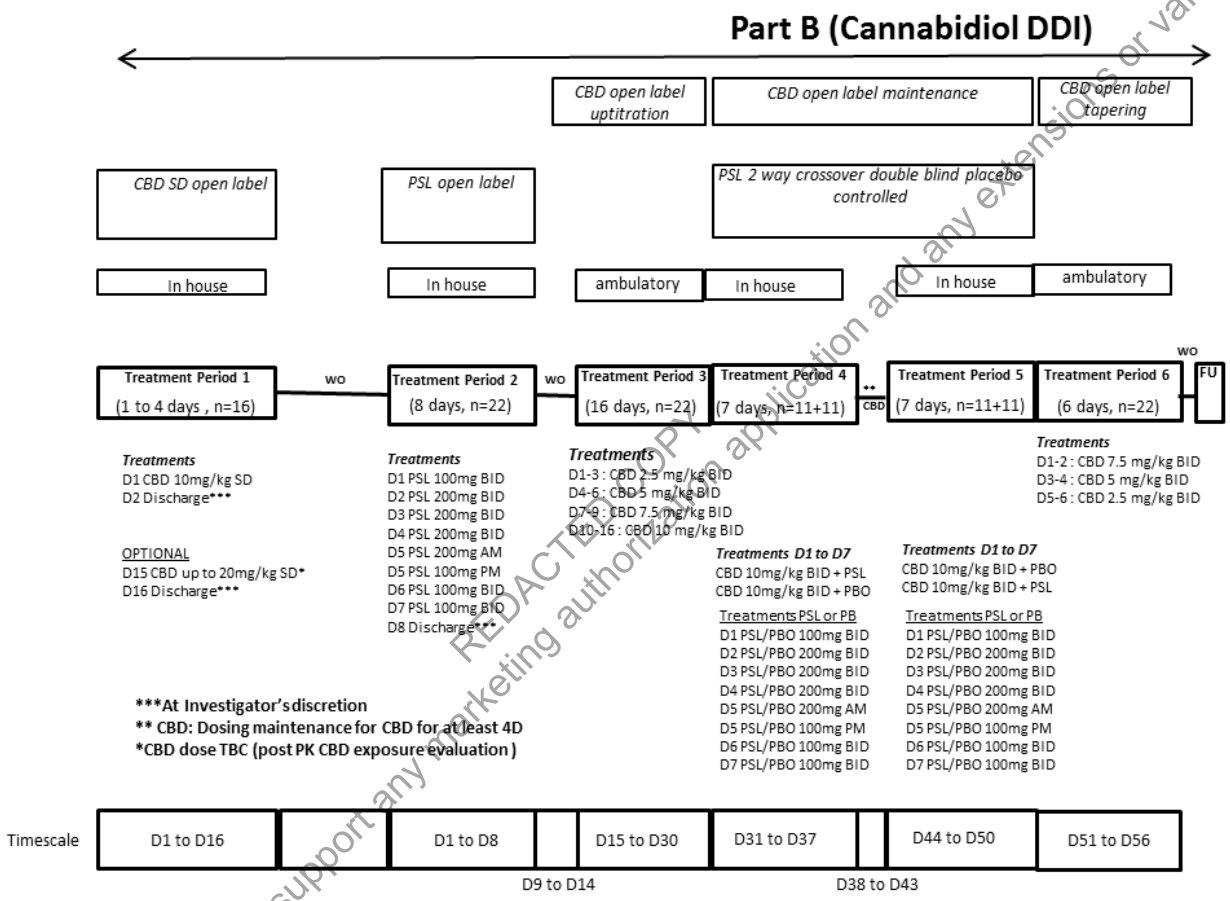
A detailed schematic diagram of the study is provided in Figure 1-1.

Figure 1-1: Study schematic – Part A



BID=twice daily; CBD=cannibidiol; D=day; FU=Follow-up Period; PBO=placebo; PSL=padsevonil; W=week
Note: Follow up will occur between 7 to 10 days after the final dose of PSL.
Note: A WO of at least 2 days will occur between Treatment Period 2 and Treatment Period 3.

Figure 1-2: Study schematic – Part B



Note: Follow up will occur between 7 to 10 days after the final dose of CBD.
Note: A WO of at least 6 days will occur following Treatment Period 1 and Treatment Period 2.
BID=twice daily; CBD=cannabidiol; D=day; FU=Follow-up Period; PBO=placebo for PSL; PSL=padsevonil; SD=single dose; W=week

1.3 Schedule of activities

1.3.1 Part A

For Part A, the schedule of activities is provided in Table 1-1 for Screening and Treatment Periods 1 and 2, in Table 1-2 for Treatment Period 3, in Table 1-3 for Treatment Periods 4 and 5, and in Table 1-4 for Treatment Period 6 and the SFU Visit.

Table 1-1: Assessment schedule Part A: Screening & Treatment Periods 1 and 2

Study Period	Screening		Treatment Period 1 and 2													
Study day	-28 to -2	D-1 [a]	D1													D2
Time related to morning IMP administration			Pre-ethanol dose	-30 m	0 h	30 m	1 h	2 h	2.5 h	3 h	4 h	5 h	6 h	8 h	10 h	24 h
Informed consent	X															
Medical history	X	X														
Previous/concomitant med	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychiatric/mental status	X		X													
Physical examination [b]	X		X													X
Body weight and height [c]	X		X													
Urine drug screen/breath alcohol test [d]	X	X														
Pregnancy test [e]	X	X														
FSH test [f]	X															
Hem/chem/urine/ serol.	X [g h]	X														X
C-SSRS [i]	X		X													X [j]
Vital signs (BP, HR, RR, T) [k]	X		X						X							X
Triplicate 12-lead ECG	X		X						X							X
VAS alcohol intoxication	X [l]		X			X	X	X		X	X	X	X	X	X	
NeuroCart [m]	X [l]		X			X	X	X		X	X	X	X	X	X	
Arrival at the clinic		X														
Urine sampling (blank aliquot)			X [n]													

Table 1-1: Assessment schedule Part A: Screening & Treatment Periods 1 and 2

Study Period	Screening		Treatment Period 1 and 2													
Study day	-28 to -2	D-1 [a]	D1													D2
Time related to morning IMP administration			Pre-ethanol dose	-30 m	0 h	30 m	1 h	2 h	2.5 h	3 h	4 h	5 h	6 h	8 h	10 h	24 h
Sample collection for exploratory genotype analysis			X [n]													
Ethanol breath sampling [o]			X													
Ethanol/placebo infusion [p]				X												
Discharge																X [j]

AE=adverse event; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; FSH=follicle stimulating hormone; h=hours; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibody; HR=heart rate; m=minutes; PK=pharmacokinetic; PSL=Padsevonil; RR=respiratory rate; T=body temperature; VAS=Visual Analog Scale

[a] Refers to D-1 (Admission) prior to Part A Treatment Period 1 only.

[b] A complete physical examination will be conducted at Part A Screening. A brief physical examination will be conducted at all other visits, including at discharge prior to the release of study participants.

[c] Height measured only at Screening. Body weight will be measured at Part A Screening and predose in Part A Treatment Period 1 and 2.

[d] All study participants will have a urine drug screen/breath alcohol test at admission. For study participants who are discharged between Treatment Periods, a urine drug screen/breath alcohol test will be performed at re-admission at the discretion of the PI.

[e] For women of childbearing potential: A serum beta-HCG pregnancy test will be performed at Screening and urine beta HCG will be performed either on the first day of each treatment period or the day before the first day of each Treatment Period at discretion of Investigator. In either case, the results must be negative prior to dosing study participants.

[f] Female study participants of non-childbearing potential to confirm postmenopausal status.

[g] Virus serology (HIV-1/2Ab, HBsAg, and HCV-Ab) only at Screening.

[h] Fasted conditions only at Screening.

[i] At the Screening Visit, "Baseline/Screening" version of the C-SSRS will be completed. At all other visits, "Since Last Visit" version of the C-SSRS will be completed.

[j] In Part A Treatment Period 2 only.

[k] Vital signs will be taken in a supine/standing position at Screening, and in a supine position at all other assessments.

[l] PD training session for all study participants. Training session will be performed at the Screening visit or during a separate visit. Baseline PD assessment will be collected as a duplicate at D1 predose. Final Baseline score will be averaged (from duplicate values).

[m] NeuroCart assessments in Part A consist of the following tests: Body Sway, VAS mood & alertness (Bond & Lader), VAS feeling high, internal- and external perception (Bowdle), SEM, Adaptive tracking, and Smooth Pursuit Eye Movements. NeuroCart assessments are taken twice at least 30 minutes prior to dosing and singlicate postdose at 30 minutes, 1, 2, 3, 4, 5, 6, 8, and 10 hours.

[n] Part A Treatment Period 1 only prior to ethanol dosing.

[o] During the ethanol/dummy infusion, the infusion rate will be adjusted based on ethanol breath sampling.

[p] Continuous infusion will begin with a 30 minute loading phase (prior to 0 hours) and will continue for 5 hours.

Table 1-2: Assessment schedule Part A: Treatment Period 3

Study Period	Treatment Period 3				
Study day	**D -1[a]**	**D1**	**D2**	**D3**	**D4**
Arrival at the clinic	X				
Previous/concomitant med	X	X	X	X	X
Urine drug screen/breath alcohol test [b]	X				
Pregnancy test [c]	X				
Adverse events	X	X	X	X	X
Psychiatric/mental status		X	X	X	X
Hem/chem/urine e	X				
C-SSRS [d, e]		X			
Brief physical examination		X [e]	X	X	X
Supine vital signs (BP, RR, HR, T) [f]		X			X
Triplicate 12-lead ECG f		X			X
PSL administration [g]		X	X	X	X
PSL trough PK sampling [e]		X	X	X	X

AE=adverse event; BID=twice daily; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; HR=heart rate; PK=pharmacokinetic; PSL=Padsevonil; T=body temperature; RR=respiratory rate; VAS=Visual Analog Scale

[a] A washout period of at least 2 days will occur between Part A Treatment Period 2 and Part A Treatment Period 3. Study participants will be re-admitted in Part A Treatment Period 3.

[b] Performed at the discretion of the PI.

[c] For women of childbearing potential: Urine beta HCG will be performed either on the first day of the treatment period or the day before the first day of the Treatment Period at discretion of Investigator. The results must be negative prior to dosing study participants.

[d] "Since Last Visit" version of the C-SSRS will be completed.

[e] Prior to IMP morning administration.

[f] Prior to and 2.5 hours after morning IMP administration (0 hours).

[g] D1: PSL 100mg BID; D2: PSL 200mg BID; D3: PSL 200mg BID; D4: PSL 200mg BID.

Table 1-3: Assessment schedule Part A: Treatment Periods 4 and 5

Study Period	Treatment Period 4 and 5																
Study day	D5 / D7																D6/ D8
Time related to Padsevonil/placebo administration	Pre-ethanol dose	-30 m	0 h	15 m	30 m	1 h	1.5 h	2 h	2.5 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h	24 h
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous/concomitant med	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hem/chem/urine	X [a]																
C-SSRS [b]	X [a]																
Psychiatric/mental status	X																X
Brief physical examination	X [a]																X
Body weight	X																
Supine vital signs (BP, HR, RR, T)	X								X								X
Triplicate 12-lead ECG	X								X								X
Ethanol breath sampling [c]	X																
Ethanol/placebo infusion [d]		X															
PSL administration [e]			X													X	X
PSL PK trough sampling [f]	X			X	X	X	X	X	X	X	X	X	X	X		X	X
Start/stop urine collection		X															
VAS alcohol intoxication	X				X	X		X		X	X	X	X	X	X		
Neurocart [g]	X				X	X		X		X	X	X	X	X	X		

AE=adverse event; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; h=hours; HR=heart rate; m=minutes; PK=pharmacokinetic; PSL=Padsevonil; T=body temperature; RR=respiratory rate; VAS=Visual Analog Scale

[a] On Day 5 in Part A Treatment Period 4. Hem/Chem/urine safety lab: to be collected the day before dosing (P3D4).

[b] "Since Last Visit" version of the C-SSRS will be completed.

[c] During the ethanol/placebo infusion, the infusion rate will be adjusted based on ethanol breath sampling.

[d] Continuous infusion will begin with a 30 minute loading phase and will continue for 5 hours. To avoid local pain, an additional glucose 5% solution will be infused in parallel for approximately 10 minutes at the start of the ethanol/dummy infusion.

[e] D5: PSL 200mg BID; D6: PSL 200mg BID; D7: PSL 200mg AM and PSL 100mg PM; D8: PSL 100mg BID

[f] Prior to morning IMP administration (0 hours).

[g] NeuroCart assessments in Part A consist of the following tests: Body Sway, VAS mood & alertness (Bond & Lader), VAS feeling high, internal- and external perception (Bowdle), SEM, Adaptive tracking, and Smooth Pursuit Eye Movements. NeuroCarts assessments are taken twice at least 30 minutes prior to dosing and singlicate postdose at 30 minutes, 1, 2, 3, 4, 5, 6, 8, and 10 hours.

Table 1-4: Assessment schedule Part A: Treatment Period 6 and SFU Visit

Study Period	Treatment Period 6		SFU Visit [a]
Study day	D9	D10	
PSL administration [b]	X		
Adverse events	X	X	X
Previous/concomitant med	X	X	X
Psychiatric and mental status	X	X	X
Supine vital signs (BP, RR, HR, T) [c]		X	X
Triplicate 12-lead ECG [d]		X	
C-SSRS [e]		X	X
Physical examination [d]		X	X
Hem/chem/urine		X	X
Discharge from the clinic [f]		X	
Pregnancy test [g]		X	

AE=adverse event; BID=twice daily; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; HR=heart rate; PK=pharmacokinetic; PSL=Padsevonil; SFU=Safety Follow-up; T=body temperature; RR=respiratory rate; VAS=Visual Analog Scale

[a] Study participants will return for a SFU Visit between 7 to 10 days after the final dose of PSL in Part A.

[b] D9: PSL 100mg BID

[d] Brief physical exams will be conducted during Part A Treatment Period 6. A full physical exam will be conducted at the SFU Visit.

[d] Prior to and 2.5 hours after morning IMP administration (0 hours).

[e] "Since Last Visit" version of the C-SSRS will be completed.

[f] Study participants will be discharged in the morning on Day 11 following the completion of all assessments.

[g] For women of childbearing potential: Urine beta HCG will be performed.

1.3.2 Part B

For Part B, the schedule of activities is provided in Table 1-5 for Treatment Period 1, Table 1-6 for Treatment Period 2, Table 1-7 for Treatment Period 3, Table 1-8 for Treatment Periods 4 and 5, and Table 1-9 for Treatment Period 6 and the SFU Visit.

Table 1-5: Assessment schedule Part B: Screening & Treatment Period 1

Study Period	Screening		Treatment Period 1 [a]	
Study day	**-28 to -2**	**D-1 [b]**	**D1/D15 (Optional) [c]**	**D2/D16 (Optional) [d]**
Informed consent	X			
Medical history	X	X		
Previous/concomitant med	X	X	X	X
Adverse events	X	X	X	X
Psychiatric/mental status	X		X	X
Physical examination [e]	X		X	X
Body weight and height	X			
Urine drug screen/breath alcohol test [f]	X	X		
Pregnancy test [g]	X	X		
FSH test [h]	X			
Hem/chem/urine/ serol. [i]	X	X		X
C-SSRS [j]	X		X	X
Vital signs (BP, HR, RR, T) [k]	X		X	X
Triplicate 12-lead ECG	X		X	X
NeuroCart [l]	X [m]		X	X
Arrival at the clinic		X		
CBD administration [n]			X	X
CBD PK sampling [o]			X	X
Discharge				X

AE=adverse event; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; FSH=follicle stimulating hormone; h=hours; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibody; HR=heart rate; m=minutes; PK=pharmacokinetic; PSL=Padsevonil; RR=respiratory rate; SD=single dose; T=body temperature; VAS=Visual Analog Scale

[a] Assessments will be taken under fasted conditions at Screening, Day 1, and optional Day 15 only.
[b] Refers to D-1 (Admission) prior to Part B Treatment Period 1.
[c] An optional second dose of CBD may be administered on Day 15 after evaluation of PK/safety data at the discretion of the Sponsor.
[d] A washout of at least 6 days will occur between Treatment Period 1 and Treatment Period 2.
[e] A complete physical examination will be conducted at Screening. A brief physical examination will be conducted at all other visits, including at discharge prior to the release of study participants.
[f] All study participants will have a urine drug screen/breath alcohol test at admission. For study participants who are discharged between treatment periods, a urine drug screen/breath alcohol test will be performed at re-admission at the discretion of the PI.
[g] For women of childbearing potential: A serum beta-HCG pregnancy test will be performed at Screening and urine beta HCG will be performed either on the first day of each treatment period or the day before the first day of each treatment period at discretion of Investigator. In either case, the results must be negative prior to dosing study participants.
[h] Female study participants of non-childbearing potential to confirm postmenopausal status.
[i] Virus serology (HIV-1/2Ab, HBsAg, and HCV-Ab) only at Screening.
[j] At the Screening Visit, "Baseline/Screening" version of the C-SSRS will be completed. At all other visits, "Since Last Visit" version of the C-SSRS will be completed.
[k] Vital signs will be taken in a supine/standing position at Screening, and in a supine position at all other assessments.
[l] NeuroCart assessments in Part B consist of the following tests: Body Sway, VAS mood & alertness (Bond & Lader), VAS feeling high, internal- and external perception (Bowdle), SEM, and Smooth Pursuit Eye Movements.
[m] PD training session for all study participants. Training session will be performed at Screening or during a separate visit. Baseline PD assessment will be collected as a duplicate at D1 predose. Final Baseline score will be averaged (from duplicate values).
[n] D1: CBD 10mg/kg SD; D15 (optional): CBD dose to be defined (within 5 and 20mg/kg SD)
[o] CBD PK sampling will occur at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8,12 and 24 hours postdose.

Table 1-6: Assessment schedule Part B: Treatment Period 2

Study Period	Treatment Period 2 [a] [b]							
Study day	**D -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7/D8**
Adverse events	X	X	X	X	X	X	X	X
Psychiatric and mental status		X	X	X	X	X	X	X
Previous/concomitant med	X	X	X	X	X	X	X	X
Arrival at clinic	X							
Urine drug screen/ breath alcohol test [l]	X							
Urine sampling (blank aliquot) [c]	X							
Pregnancy test [d]	X							
Hem/chem/urine [c]	X	X			X			X
Neurocart								
C-SSRS [e]		X						X [f]
Brief physical examination		X			X			X [f]
Supine vital signs (BP, RR, HR, T) [g]		X			X	X	X	X [f]
Triplicate 12-lead ECG [g]		X			X	X	X	X [f]
PSL administration [h]		X	X	X	X	X	X	X
PSL PK trough sampling [c] [i]		X	X	X	X	X	X	X
NeuroCart [j]	X					X		
Urine sampling (blank aliquot) [c]	X							
Sample collection for exploratory genotype analysis [c]	X							
Start/stop urine collection						X [k]		
Discharge								X [f]

Table 1-6: Assessment schedule Part B: Treatment Period 2

Study Period	Treatment Period 2 [a] [b]							
Study day	D -1	D1	D2	D3	D4	D5	D6	D7/D8

AE=adverse event; BID=twice daily; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; h=hour; HR=heart rate; PK=pharmacokinetic; PSL=Padsevonil; RR=respiratory rate; T=body temperature; SEM=Saccadic Eye Movements; VAS=Visual Analog Scale

[a] For study participants that begin Part B in Treatment Period 2, Screening assessments will be performed according the Screening assessments described in Table 1-5.

[b] A washout of at least 6 days will occur at the end of Treatment Period 2 prior to Treatment Period 3 in Part B.

[c] Prior to IMP administration.

[d] For women of childbearing potential: A urine beta HCG will be performed either on the first day of the treatment period or the day before the first day of the treatment period at discretion of Investigator. The result must be negative prior to dosing study participants.

[e] "Since Last Visit" version of the C-SSRS will be completed.

[f] In Treatment Period 2, on Day 9 only.

[g] Prior to and 2.5 hours after morning IMP administration.

[h] D1: PSL 100mg BID; D2: PSL 200mg BID; D3: PSL 200mg BID; D4: PSL 200mg BID; D5: PSL 200mg AM; D5: PSL 100mg PM; D6: PSL 100mg BID; D7: PSL 100mg BID

[i] Blood samples for measurement of plasma concentration of PSL will be obtained at the following times: predose (within 5 minutes of dosing), and at Day 5 (PK day) postdose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose.

[j] NeuroCart assessments in Part B consist of the following tests: Body Sway, VAS mood & alertness (Bond & Lader), VAS feeling high, internal- and external perception (Bowdle), SEM, and Smooth Pursuit Eye Movements. NeuroCarts assessments are taken twice at least 30 minutes prior to dosing and singlicate postdose at 30 minutes, 1, 2, 3, 4, 5, 6, 8, and 10 hours.

[k] Urine collection for additional PK analysis will be collected for 12-hours post-morning dose on Day 5.

Table 1-7: Assessment schedule Part B: Treatment Period 3

Study Period		Treatment Period 3 [a]															
Study day	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**
Previous/concomitant meds [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychiatric and mental status		X			X			X			X						X
Urine drug screen/breath alcohol screen [b c]		X			X			X			X						X
Pregnancy test [d]		X			X			X			X						X
Brief physical examination [c]		X			X			X			X						
Hem/chem/urine [c]	X							X									X
Supine Vital signs (BP, RR, HR, T) [e]		X			X			X			X						
Triplicate 12-lead ECG [e]		X			X			X			X						
C-SSRS [f]		X															
CBD administration [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBD PK trough sampling [c]		X			X			X			X						X
NeuroCart [h]	X																X
Arrival at the clinic		X			X			X			X						X

AE=adverse event; BID=twice daily; BP=blood pressure; CBD=cannabidiol; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; h=hour; HR=heart rate; PK=pharmacokinetic; PSL=Padsevonil; RR=respiratory rate; SEM=Saccadic Eye Movements; T=body temperature; VAS=Visual Analog Scale; W=Week

[a] A washout of at least 6 days will occur prior to the start of Treatment Period 3.
[b] Performed at the discretion of the PI.
[c] Prior to morning CBD administration.
[d] Urine beta HCG will be collected either on the first day of the treatment period or the day before the first day of the treatment period at discretion of Investigator. In either case, the result must be negative prior to dosing study participants.
e Prior to and 2.5 hours after morning CBD administration.
[f] "Since Last Visit" version of the C-SSRS will be completed.
[g] Days 1 to 3: CBD 2.5mg/kg BID; Days 4 to 6: CBD 5mg/kg BID; Days 7 to 9: CBD 7.5mg/kg BID; Days 10 to 16: CBD 10mg/kg BID (doses to be confirmed from CBD PK exposure in Treatment Period 1).
[h] NeuroCart assessments in Part B consist of the following tests: Body Sway, VAS mood & alertness (Bond & Lader), VAS feeling high, internal- and external perception (Bowdle), SEM, and Smooth Pursuit Eye Movements. NeuroCarts assessments are taken twice at least 30 minutes prior to dosing and singlicate postdose at 30 minutes, 1, 2, 3, 4, 5, 6, 8, and 10 hours.

Table 1-8: Assessment schedule Part B: Treatment Period 4 and 5

Study Period	Treatment Periods 4 & 5						
Study day	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**
Previous/concomitant med [a]	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Psychiatric and mental status	X	X	X	X	X	X	X
Brief physical examination a	X	X	X	X	X	X	X
Supine vital signs (BP, RR, HR, T) [b]	X	X	X	X	X	X	X
CBD 10 mg/kg BID [c]	X	X	X	X	X	X	X
PSL/placebo administration [d]	X	X	X	X	X	X	X
CBD PK trough sampling [e]	X	X	X	X	X	X	X
PSL PK trough sampling [f]	X	X	X	X	X	X	X
Triplicate 12-lead ECG b	X			X	X	X	X
C-SSRS [g]	X						X
NeuroCart [h]	X				X		
Start/stop urine collection [i]					X		
Hem/chem/urine a							X

AE=adverse event; BID=twice daily; BP=blood pressure; CBD=cannabidiol; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; h=hour; HR=heart rate; PK=pharmacokinetic; PSL=Padsevonil; RR=respiratory rate; SEM=Saccadic Eye Movements; T=body temperature; VAS=Visual Analog Scale

Note: A washout of at least 4 days will occur between Treatment Periods 4 and 5 for PSL.

[a] Prior to PSL/placebo/CBD administration.

[b] Prior to and 2.5 hours after IMP administration.

[c] CBD maintenance 10mg/kg BID (dose to be confirmed from CBD PK exposure in Treatment Period 1) between Treatment Period 4 and Treatment Period 5 for 4 Days (study participants in house).

[d] D1: PSL 100mg BID; D2: PSL 200mg BID; D3: PSL 200mg BID; D4: PSL 200mg BID; D5: PSL 200mg AM; D5: PSL 100mg PM; D6: PSL 100mg BID; D7: PSL 100mg BID.

[f] Blood samples for measurement of plasma concentration of PSL and CBD will be obtained at the following times: predose (within 5 minutes of dosing), and at Day 5 (PK day) postdose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose.

[g] "Since Last Visit" version of the C-SSRS will be completed.

[h] NeuroCart assessments in Part B consist of the following tests: Body Sway, VAS mood & alertness (Bond & Lader), VAS feeling high, internal- and external perception (Bowdle), SEM, and Smooth Pursuit Eye Movements. NeuroCarts assessments are taken twice at least 30 minutes prior to dosing and singlicate postdose at 30 minutes, 1, 2, 3, 4, 5, 6, 8, and 10 hours.

[i] Urine samples for additional PK analysis will be collected 12-hours postdose on Day 5.

Table 1-9: Assessment schedule Part B: Treatment Period 6 and SFU

Study Period	Treatment Period 6						SFU Visit [a]
Study day	D1	D2	D3	D4	D5	D6/D7	
Adverse events	X	X	X	X	X	X	X
Previous/concomitant meds	X	X	X	X	X	X	X
Hem/chem/urine [b]						X	X
Supine vital signs (BP, RR, HR, T) [c]	X		X			X [d]	X
Psychiatric and mental status	X		X			X	X
Triplicate 12-lead ECG [c]	X		X			X [d]	X
C-SSRS [e]	X					X [d]	X
CBD administration [f]	X	X	X	X	X	X	
CBD PK trough sampling b	X		X			X	X
Physical examination [g]	X		X			X [d]	X
Pregnancy test						X [h]	
Discharge	X					X [d]	

AE=adverse event; BID=twice daily; BP=blood pressure; CBD=cannabidiol; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; h=hour; HR=heart rate; PK=pharmacokinetic; PSL=Padsevonil; RR=respiratory rate; SAE=serious adverse event; T=body temperature; VAS=Visual Analog Scale; W=Week

[a] Study participants will return for a SFU Visit between 7 to 10 days after the final dose of CBD in Part B.

[b] Prior to CBD administration.

[c] Prior to and 2.5 hours after morning IMP administration.

[d] Study participants will be discharged in the morning on Day 7 following the completion of all assessments.

[e] "Since Last Visit" version of the C-SSRS will be completed.

[f] Days 1 to 2: CBD 7.5mg/kg BID; Days 3 to 4: CBD 5mg/kg BID; Days 5 to 6: CBD 2.5mg/kg BID (doses to be confirmed from CBD PK exposure in Treatment Period 1).

[g] Brief physical exams will be conducted during Part B Treatment Period 6. A full physical exam will be conducted at the SFU Visit.

[h] For women of childbearing potential: Urine beta HCG will be performed.

2 INTRODUCTION

2.1 Study rationale

Padsevonil is a novel chemical entity with selective affinity for both presynaptic vesicle protein 2 isoforms and postsynaptic cBZR sites on the $GABA_A$ receptor that has shown compelling, broad-range efficacy in several preclinical models of epilepsy conducted by UCB. Padsevonil is cleared via metabolism involving the CYP pathway; the formation of the 2 major metabolites, [redacted], is mainly mediated by CYP3A4, with potential involvement of CYP2C19. Drug-drug interactions that result in alterations in the PK of AEDs can have a profound impact on tolerability, efficacy, and safety, and can potentially result in toxicity. It is therefore important to consider and estimate at an early stage the possible interactions that may occur with the concomitant use of PSL and other drugs.

UP0071 is designed to characterize the PK/PD of steady-state PSL in healthy study participants receiving either ethanol or steady-state treatment of CBD. Considering the central nervous system (CNS) effect of ethanol, PD interaction between PSL and ethanol is plausible. However, it is difficult to predict the potential impact of the combination. Cannabidiol is a major chemical of marijuana that does not possess psychoactive properties. There seems to be a growing body of basic pharmacologic data suggesting there may be a role for CBD, especially in the treatment of refractory epilepsy. As PSL and CBD share the same P450 CYP pathway and aim to treat the same patient population, a clinical study investigating the potential PD and PK interaction is useful.

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

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

Compounds binding to 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 1 of these mechanisms. Preclinical data in animal models of epilepsy support this assumption with compelling synergistic interaction observed between LEV and AEDs with GABAergic mechanisms of action (Kaminski et al, 2009). This synergistic interaction was particularly pronounced when combinations of LEV and benzodiazepines were tested and a significant increase in anticonvulsant potency of these drugs was observed associated with a higher therapeutic index.

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

2.3 Benefit/risk assessment

Overall, the clinical pharmacology and clinical studies in drug-resistant epilepsy demonstrated the AE profile of PSL is generally consistent with the pharmacological activity of the product, and as expected in the context of early dose-escalation studies in healthy study participants and patients with epilepsy. The safety findings to date suggest that the AEs experienced by study participants receiving single and repeated doses of PSL are limited principally to CNS effects. The AEs tend to be dose-related in frequency and intensity, self-limiting, and tend to decrease in intensity over the first few days of dosing.

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

Despite the occurrence of several electrocardiogram (ECG) findings (including different types of ectopy) both in healthy study participants and study participants with epilepsy, an independent expert cardiologist reviewed data from Phase 1 and Phase 2 and determined that none of these findings were assessed as being likely to be related to PSL. No clinically significant echocardiographic findings (only minor/trace or Grade 1 findings) have been observed in studies EP0069 and EP0073 and all echocardiograms were assessed as normal. There are currently no data to suggest that the drug has an adverse effect on cardiovascular function other than a minimal lowering effect on blood pressure. The degrees of reduction seen in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are consistent with the $GABA_A$-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use. As a precaution, and in view of the nonclinical histopathological (microscopic) 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 adverse events of PSL may be found in the Investigator's Brochure (IB). The current IB reflects the safety profile of PSL as it is known and may change with the accumulation of additional data.

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

3 OBJECTIVES AND ENDPOINTS

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

Table 3-1: Study objectives and endpoints

Objectives	Endpoints
Primary	
• Part A: To evaluate the PD interaction between steady-state treatment with PSL and ethanol	• Smooth pursuit (%) to assess eye movement coordination and attention
• Part B: To evaluate the PK interaction between steady-state treatment with PSL and CBD	• $C_{max,ss}$ and AUC_{τ} obtained from the plasma concentration-time profiles for PSL and CBD
Secondary	
• Part A: To evaluate the PK interaction between steady-state treatment with PSL and ethanol	• Ethanol dose infused over time • $C_{max,ss}$ and AUC_{τ} obtained from the plasma concentration-time profiles for PSL
• Part B: To evaluate the PK interaction between steady-state treatment with PSL and CBD	• $t_{1/2}$, and $CL_{ss/F}$ obtained from the plasma concentration-time profiles for PSL and CBD
• Parts A and B: To evaluate the PD interaction between steady-state treatment with PSL and ethanol or between steady-state treatment with PSL and CBD	• Smooth pursuit (%) to assess eye movement coordination and attention (Part B only) • Saccadic peak velocity (degrees/sec) to assess sedation • Adaptive tracking (%) to assess visuo-motor control and vigilance • Body Sway to assess postural stability
• Parts A and B: To evaluate the safety and tolerability of PSL in study participants receiving concomitant ethanol or CBD	• Adverse events (AEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation of the study
Other	
• Parts A and B: To evaluate the safety and tolerability of PSL in study participants receiving concomitant ethanol or CBD	• Vital signs (pulse rate, respiratory rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) • 12-lead electrocardiogram (ECG) parameters • Physical examination findings • Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)

• Parts A and B: To evaluate the PD interaction between steady-state treatment with PSL and ethanol or steady-state treatment with PSL and CBD	• Visual analogue scales (VAS) Bond & Lader to assess study participantive alertness, mood, and calmness • VAS feeling high, internal and external perception (Bowdle) • VAS for alcohol intoxication to assess study participantive effects of ethanol (Part A only)
• Part B: To evaluate the PK interaction between steady-state treatment with PSL and CBD	• t_{max} obtained from the plasma concentration-time profiles for PSL and CBD • $C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,}$ and metabolite/parent (based on $C_{max,ss}$ and AUC_{τ}) obtained from the plasma concentration-time profiles for PSL metabolites and CBD active metabolite
• Part A and B: To collect and store blood for potential ADME genotype (if needed)	• Possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL (and metabolite) PK analyses, if needed
• Part A and B: To collect urine samples for additional PK analyses depending on the outcome of PSL (and metabolite) PK analyses, if needed	• Urine sample PK analysis

4 STUDY DESIGN

4.1 Overall design

This is a Phase 1, double-blind, randomized, placebo-controlled, single-center, cross-over study to evaluate the PK, PD, safety, and tolerability of steady state treatment of PSL in healthy study participants receiving either ethanol (Part A) or steady-state treatment of CBD (Part B). The study design is shown in Figure 1-1.

A study participant who provides written informed consent will be screened within 28 days before the first Treatment Period in Part A or Part B. Study participants that complete Part A of the study are not eligible to complete Part B; similarly, study participants that complete Part B are not eligible to complete Part A.

4.1.1 Part A

Treatment Periods 1 and 2, and 4 and 5 are 2-way cross-over, placebo-controlled, ethanol-clamping periods with a washout of at least 2 days between Treatment Periods 2 and 3; PSL is not administered in Treatment Periods 1 and 2. Treatment Period 3 is an open-label PSL up titration period toward a maintenance level of 200mg BID, and is immediately followed by

Treatment Period 4 and Treatment Period 5. Treatment Period 6 is the PSL tapering open-label period. See Section 1.3.1 for the schedule of activites for Part A.

During each cross-over period, the study participant will check into the clinic the evening prior to the day of administration of ethanol/dummy infusion and PSL (Day -1). On Day 1 of Treatment Periods 1, 2, 4 and 5, a continuous infusion of ethanol or dummy infusion will begin with a 30 minute loading phase and will continue for 5 hours. On Day 1 of Treatment Periods 4 and 5, PSL will be administered immediately after the end of the loading phase.

During the first 10 minutes, the infusion will be accompanied by an infusion of 5% glucose via the same line in order to mask the sensation at the beginning of the ethanol infusion. The ethanol infusion rate is initially based on weight, height, age, and sex. The infusion rate is determined based on the Watson estimate of body water (Watson et al, 1980). Subsequently, the infusion rate will be adjusted based on breath ethanol measurements to maintain breath ethanol levels (and by extension, blood ethanol levels) of 0.6g/L. Following administration of PSL, the study participant will be observed for approximately 24 hours.

4.1.2 Part B

Treatment Period 1 of Part B will be conducted in a sentinel cohort of healthy study participants in order to evaluate CBD safety and PK exposure under a single dose of CBD 10mg/kg (fasted conditions). The results of the PK analysis will be compared to published PK data of CBD (dose of 750mg in fasted conditions) obtained in similar conditions with Epidiolex® (Taylor et al, 2018). The decision to continue on with the rest of Part B or terminate the study following the first CBD dose in Treatment Period 1 of Part B will be made pending the outcome of the analysis of CBD safety and exposure. A difference between the PK results in the present study and the literature findings requiring a >2-fold dose adjustment will be considered as not manageable and would result in termination of the study. If a dose adjustement ≤2-fold is needed, then the study will proceed with the second dose of CBD of Treatment Period 1 in Part B. If the observed CBD exposure matches the data from the literature, then study will proceed directly to Treatment Period 2 of Part B (no second dosing of CBD will be required). Treatment Period 2 cannot commence until the results from Treatment Period 1 are analyzed.

A washout of at least 6 days will occur between Treatment Period 1 and Treatment Period 2. Treatment Period 2 will include 7 days of treatment with open-label PSL treatment. Treatment Period 3 starts after a washout of minimally 6 days for all study participants, and includes an ambulatory open-label CBD up titration of 16 days toward a maintenance level of 10mg/kg BID.

Treatment Periods 4 and 5 are 2-way cross-over, double-blind and placebo-controlled periods with PSL up titrated to a maintenance level of 200mg BID through Day 5 and subsequent down titration until Day 8. A maintenance dose of 10mg/kg BID CBD will occur in-house between Treatment Periods 4 and 5. Cannabidiol down titration starts in Treatment Period 6.

Study participants will be discharged at the end of Treatment Period 6 and return for a SFU Visit 7 to 10 days after the final dose of CBD. See Section 1.3.2 for the schedule of activities for Part B.

4.2 Scientific rationale for study design

4.2.1 Part A

Considering the CNS effect of ethanol, a PD interaction between PSL and ethanol is plausible. Nonetheless, it is difficult to predict the potential impact of the combination. However, knowing the elimination pathways of both PSL (mainly CYP3A4) and ethanol (CYP2E1, alcohol dehydrogenase) as well as their perpetrator profiles, it is unlikely that a PK interaction between PSL and ethanol will occur.

The interaction between ethanol and PSL will be assessed under PSL at steady state. This is deemed to be more clinically relevant and should reduce the risk of having serious AEs when combined with ethanol. Indeed, healthy study participants have demonstrated better tolerability to PSL after 2 to 3 days of repeated dosing. A study in patients with epilepsy is not possible as most common AEDs have recommendations in their label regarding avoiding alcohol intake.

4.2.2 Part B

Cannabidiol is a major chemical of marijuana that does not possess psychoactive properties. There seems to be a growing body of data suggesting there may be a role for CBD, especially in the treatment of refractory epilepsy (Devinsky et al, 2017; Devinsky et al, 2018). Cannabidiol is well tolerated in humans, with doses up to 600mg not resulting in psychotic symptoms (Taylor et al, 2018). Following single doses in humans, the half-life of CBD when taken orally is about 1 to 2 days (Devinsky et al, 2014). In vitro studies have shown that CBD is a potent inhibitor of multiple CYP isozymes, including CYP2C19 and CYP3A4 (Zhornitsky and Potvin, 2012). As PSL and CBD share some of the same enzymatic pathways and aim to treat epilepsy populations, a clinical study investigating the potential PD and PK interactions would be useful.

Padsevonil will be up titrated to a maintenance dose of 200mg BID (1 of the clinical doses administered in the global studies). Assessments will take place after 4 days of dosing to allow for maximum CYP2C19 inhibition. The PK of CBD will be evaluated in a sentinel cohort of at least 16 healthy study participants in Part B to assess the safety and exposure of CBD formulations prior to PSL dosing.

4.3 Justification for dose

The dosages of PSL for this study will be 100mg, 100mg BID, and 200mg BID. These are several of the doses being evaluated in the late phase development program and, while lower than the maximum tolerated dose (MTD; 400mg BID), are considered adequate for the purposes of this study while not exposing healthy study participants to the MTD.

4.3.1 Part A

Study participants will receive ethanol by infusion. The rate is initially based on weight, height, age, and sex. The infusion rate is determined based on the Watson estimate of body water with an average of approximately 60g ethanol/hour for the first 5 minutes and 45g ethanol/hour during the second 5 minutes in healthy male Caucasians. Subsequently, the infusion rate will be adjusted based on breath ethanol measurements to maintain breath ethanol levels (and by extension, blood ethanol levels) of 0.6g/L.

4.3.2 Part B

Study participants will take GMP Cannabidiol according to reference material. Cannabidiol will be provided as an oily solution (similar to Epidiolex®). The first single dose of CBD will be 10mg/kg given in fasted conditions (Treatment Period 1). This dose level is a recommended dose for Epidiolex® for the treatment of seizure associated with Lennox-Gastaut syndrome or Dravet syndrome (Devinsky et al, 2017; Devinsky et al, 2018). Following analysis of safety and PK data, this dose may be adjusted (within 2-fold) to match published exposure data obtained with Epidiolex®.

4.4 End of study definition

A study participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (see Section 1.3).

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

5 STUDY POPULATION

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

5.1 Inclusion criteria

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

Age

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

Type of participant and disease characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

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

3. Participant must have previous experience with alcohol consumption and, therefore, must be familiar with the effects and able to tolerate social amounts of alcohol.

Weight

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

Sex

5. Participants are male or female:
   - A male participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the treatment period and for at least 7 days after the last dose of study treatment and refrain from donating sperm during this period until 90 days after the last dose of study treatment.
   - A female participant is eligible to participate if she is not pregnant (see Appendix 4; Section 10.4), not breastfeeding, and at least 1 of the following conditions applies:
     - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)
       OR
       A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the Treatment Period and for at least 90 days after the last dose of study treatment.

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).
7. Participant must be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator, and is capable of communicating satisfactorily with the Investigator.

5.2 Exclusion criteria

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

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study, such as a history of schizophrenia, or other psychotic disorder, bipolar disorder, or severe unipolar depression. The presence of potential psychiatric exclusion criteria will be determined based on the psychiatric history collected at the Screening Visit.
2. Participant has history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
3. Participant has a history of chronic alcohol or drug abuse within the previous 6 months or the presence of drug or alcohol dependency at Screening or Day -1 or tests positive for alcohol and/or drugs at Screening or Day -1. In case a false positive is suspected, the alcohol or drug test may be repeated once.

   For the purposes of this study, history of chronic alcohol abuse is defined as an average weekly intake of more than 21 units or an average daily intake of more than 3 units (males),

or defined as an average weekly intake of more than 14 units or an average daily intake of more than 2 units (females). One unit is equivalent to a half-pint (220mL) of beer or 1 measure (25mL) of spirits or 1 glass (125mL) of wine.

4. Participant has a positive prestudy drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

   Note: 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).

5. Participant has a known hypersensitivity to any components of the study medication or comparative drugs (and/or an investigational device) as stated in this protocol.

6. Participant has abnormal blood pressure.

   Note: This includes both the routine and orthostatic hypotension BP assessments. For routine BP, participants must have blood pressure and PR within normal range in the supine position after 5 minutes rest (SBP: 90mmHg to 145mmHg; DBP: 40mmHg to 95mmHg; PR: 40bpm to 100bpm).

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

7. 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.

8. Participant has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.

9. Participant has lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

Prior/concomitant therapy

10. Participant has past or intended use of over-the-counter or prescription medication including herbal medications within 2 weeks or 5 half-lives prior to dosing. Specific medications listed in Section 6.5.1 may be allowed.

11. Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin etc.) within 2 months prior to dosing. In case of uncertainty, the Medical Monitor should be consulted.

Prior/concurrent clinical study experience

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

Diagnostic assessments

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

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

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

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.
15. Participant has bilirubin >1.0xULN (isolated bilirubin >1.0xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
17. Participant has any clinically relevant ECG finding at the Screening Visit or at Baseline. Study participant has an abnormality in the 12-lead ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett's formula (QTcB) or Fridericia's formula (QTcF) >450ms in participants in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval ≥220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out of range result, 1 repeat will be allowed. If out of range again, the study participant cannot be included.

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

    NOTE B: The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant.
18. Participant has other clinical laboratory test results outside the local reference ranges that are considered as clinically significant by the Investigator. In the case of uncertainty, lab parameters outside the reference ranges can be retested once. If lab parameters outside the

reference range are considered as clinically insignificant, the study participant may be allowed in the study, but such inclusions should be agreed with the UCB Study Physician.

19. Participant has the presence of hepatitis B surface antigen (HBsAg) at Screening.
20. Participant has a positive hepatitis C antibody test result at Screening. NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test is obtained
21. Participant has a positive human immunodeficiency virus (HIV) antibody test at Screening.

Other exclusions

22. Participant has made a blood or plasma donation or has had a comparable blood loss (>450mL) within the last 90 days prior to the Screening Visit. Blood donation during the study is not permitted.
23. Participant has a consumption of more than 600mg of caffeine/day (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg).
24. 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.
25. Participant ingests grapefruit, passion fruit, or pawpaw (as beverage, fruit, or supplements) within 72 hours before each administration of IMP. If this is the case at the start of the study, study participants may be rescreened.
26. Female participants tests positive for pregnancy, plans to get pregnant during the participation in the study, or who is breastfeeding.
27. Study participant has a diet that deviates notably from the "normal" amounts of protein, carbohydrate, and fat, as judged by the Investigator.
28. Study participant has undergone sudden and/or extreme changes in exercise levels for 2 weeks prior to Screening Visit.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Study participants will complete a light meal approximately 30 minutes prior to each morning dose of CBD/PSL administration and will complete a standard meal approximately 30 minutes prior to the evening dose. On days when PK assessments will be taken, study participants will complete a similar meal between periods.
- Study participants will complete assessments on the morning of Day 1 and Day 15 of Treatment Period 1 (Part B) and at Screening under fasting conditions.
- Study participants should keep their usual diet (besides the restrictions for the study) necessary for the maintenance of good health; excessive food consumption should be avoided.

- Padsevonil will be administered orally with 8oz (240mL) of water. Between 1 hour predose and 2 hours postdose, the total intake of beverages should be limited to 100mL. Water will be available ad libitum except for between 1 hour before and 2 hours after dosing.
- Study participants should refrain from consumption of grapefruit, starfruit, and pawpaw (as beverage, fruit or supplements) from 3 days before the start of study treatment until after the final dose.

5.3.2 Caffeine, alcohol, and tobacco

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

5.3.3 Activity

- Participants will abstain from strenuous exercise from 3 days prior to visit and during the study. Participants may participate in light recreational activities during the study (eg, watching television, reading, and playing table tennis).

5.4 Screen failures

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

5.4.1 Rescreening

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

- Study participant ingests grapefruit (as beverage, fruit, or supplements) within 72 hours before each administration of IMP.
- Study participant has a suspected false positive drug test.
- Study participant has a non-clinically significant vital signs measurement.
- If a study participant does meets the exclusion criteria at Screening or on Day -1 due to an out-of-range laboratory result or a minor illness, he/she can be rescreened once at the discretion of the Investigator. 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. This includes re-screening.

Rescreened 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 treatments administered is provided in Table 6-1. Further Guidance or information are provided in the IMP Handling Manual.

Table 6-1: Treatments administered

Study Treatment Name:	PSL	Placebo (for PSL)	Ethanol	Placebo (for ethanol) infusion	CBD
Dosage formulation:	Tablets	Matching PBO tablets	IV infusion	IV infusion	Solution/suspension
Unit dose strength(s)/Dosage level(s):	100mg, 100mg BID, 200mg BID	Matching PBO tablets	Alcohol 10% in Glucose 5%; Adjusted to maintain breath ethanol levels of 0.6g/L	Glucose 5%; 275mmol/L in bag of 500mL	Up to 10mg/kg BID [a]
Route of Administration	Oral	Oral	Infusion	Infusion	Oral
Dosing instructions:	Dosing instructions are provided in the "UP0071 IMP Handling Manual" (IP Instruction for Handling).				
Packaging and Labeling	PSL and matching PBO tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.		Ethanol and matching PBO are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.		CBD is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.
Manufacturer	UCB	UCB	LUMC	LUMC	EchoPharma

BID=twice per day; CBD=cannabidiol; h=hours; IP=investigational product; PBO=placebo; PK=pharmacokinetic. PSL=padsevonil; SmPC=Summary of Product Characteristics

[a] Doses to be confirmed from CBD PK exposure in Part B, Treatment Period 1.

6.2 Preparation, handling, storage, and accountability requirements

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

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

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

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

Further guidance and information for the final disposition of unused study treatment are provided in the "UP0071 IMP Handling Manual" (IP Instruction for Handling).

6.2.1 Drug accountability

A Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

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

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs 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

A contract research organization (CRO; ie, ICON) randomization biostatistician will create the program to generate the randomization code and code break envelopes for each study part. The randomization biostatistician will be independent of the study. A dummy randomization schedule will be prepared by the randomization biostatistician (for Part A: cross-over 2x2 scheme with 4 treatment sequences; for Part B: 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 in a secure environment and will be reviewed by a quality control randomization biostatistician, also independent of the study. These randomization lists (list of Part A and list of Part B) will be retained by ICON until the end of the study (ie, until after database lock). The treatment assignment will be random.

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

- Sponsor Patient Safety staff for SAE reporting (sealed envelope)
- Bioanalytical staff (to identify samples to be measured)
- Unblinded member of pharmacy involved in IMP preparation and dispensing or site quality/safety insurance
- Independent Biostatistician/Early Statistical Programmer

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

After eligibility of a participant has been confirmed, the study participants may be included and assigned to a subject number from 1 to 22 in Part A. Replacement study participants will be numbered +100 (eg, Study participant 5 will have Study participant 105 as replacement).

Similarly, for Part B, eligible study participant may be included and assigned a study participant number from 1001 to 1022. Replacement subjects will be numbered +100, e.g. Study participant 1005 will have Study participant 1105 as replacement.

In Part A and Part B, each study participant (screen failure and eligible) will receive a unique 5 digit UCB number assigned at Screening from a range of numbers supplied by UCB Clinical Data Operations, Technology, and Standards, which will serve as the UCB study participant identifier throughout the study.

Study participants that complete Part A of the study are not eligible to complete Part B; similarly, study participants that complete Part B are not eligible to complete Part A.

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 (1 for each study part) and communicate the randomization assignment to the unblinded site pharmacist. Each specific randomization number will be linked to the treatment allocation on the randomization schedule, which will be dispensed by the unblinded site pharmacist. The randomization numbers will also be recorded in the eCRF.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of treatment blind

All participant treatment details (treatments, Treatment Period, and treatment sequences) will be allocated and maintained through the use of randomization lists and emergency envelopes (or equivalent). The investigator and all study site personel will be blinded to treatment assignments during the study.

6.3.1.1.1 Ethanol and matching placebo

To maintain blinding with respect to ethanol (ethanol 10% w/v solution in 5% glucose) and ethanol placebo (5% glucose), an individual who is not a member of the study team (has no responsibilities for study participant assessments) will obtain breath ethanol concentrations and adjust the infusion rate accordingly. For study participants randomized to ethanol, the infusion assistant will use actual breath ethanol concentration measurements to adjust the infusion rate according to an algorithm. For study participants randomized to placebo, the infusion assistant will use sham breath ethanol concentrations prepared prior to the study to make sham adjustments to the infusion rate.

6.3.1.1.2 PSL and matching placebo

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

6.3.1.2 Breaking the treatment blind in an emergency situation

An emergency envelope (or equivalent) containing the randomization code will be printed for each participant in a double-blind study and must not be broken, except for emergency situations. The CPM must be informed immediately when a code is broken, but should remain blinded to specific treatment information. Any unblinding of the study medication performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

6.4 Treatment compliance

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

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- Paracetamol for the treatment of mild symptoms (eg, headache or other pain), given at most every 6h to 8h, not exceeding 2g/day, and with a total of no more than 5g over 7 days
- Inhaled corticosteroids for seasonal rhinitis
- Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

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

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

6.5.3 Rescue medication

Not applicable.

6.6 Dose modification

Dose modifications, in accordance with the Investigator and/or Sponsor, are permitted during the study for PSL and cannabidiol for an individual study participant. During the ethanol/placebo infusion, the infusion rate will be adjusted based on ethanol breath sampling.

6.7 Treatment after the end of the study

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

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

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

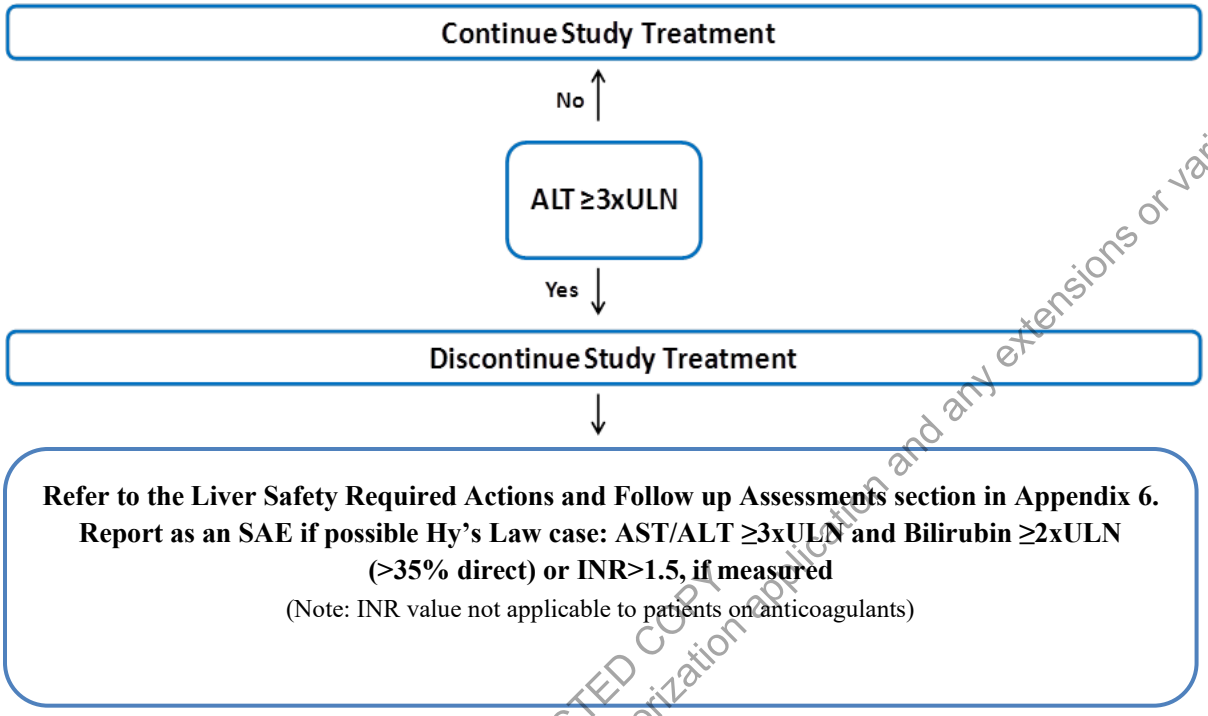
In all cases the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB Study Physician. If a participant discontinues study medication, no restart will be allowed.

7.1.1 Liver chemistry stopping criteria

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

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

Figure 7-1: Liver chemistry stopping algorithm



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

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

7.1.2 Temporary discontinuation

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

7.1.3 Criteria for study hold due to adverse events

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

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

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

- Lead to withdrawal of the affected participant

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

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

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

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

7.2 Participant discontinuation/withdrawal from the study

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

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

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

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

See the Schedule of Activities for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.

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

1. The study participant develops a clinically relevant medical condition (physical or psychiatric) that, in the opinion of the Investigator, jeopardizes or compromises the study participant's ability to participate in the study or makes it unsafe to continue.
2. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Study participant takes prohibited concomitant medications as defined in this protocol.

4. Study participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requests withdrawal of the participant.
7. Study participant has changes in the ECG that are regarded as clinically significant and/or that worsen over time. An ECG shows an absolute confirmed value for QTcB or QTcF ≥500ms or ≥60ms above Baseline.
8. Study participant develops second- or third-degree atrioventricular block or another clinically relevant change in ECG as determined by the Investigator.
9. Study participant has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The study participant should be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgment of the benefit/risk ratio of continuing the study participant in the study on PSL.
   - 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.
10. Study participant is suspected of having a serious multiorgan hypersensitivity reaction. Serious suspected multiorgan hypersensitivity cases may be identified and reported to the Sponsor by the Investigator using the following algorithm:
    - An AE or laboratory value (as defined below) suggestive of internal organ involvement including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.
    - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
    - Eosinophils percentage ≥10%
    - Eosinophils absolute ≥0.5G/L
    - Neutrophils absolute <1.5G/L
    - Platelets absolute ≤100G/L

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

For study participants considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the study participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a

narrative description of the reason(s) for removing the study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

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

Study particpants withdrawn will be replaced at the discretion of the Investigator and Sponsor.

7.3 Lost to follow up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

Protocol waivers or exemptions are not allowed.

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

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

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

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

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

The safety and tolerability of repeated doses of PSL when co-administered with single dose of ethanol or in the setting of stable concomitant therapy with CBD will be monitored by evaluation of AEs, vital signs (pulse rate, body temperature, respiratory rate, SBP, and DBP), 12-lead ECG parameters, psychiatric and mental status findings, physical examination findings, clinical laboratory test results, and suicidal risk monitoring. Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1 Physical examination

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

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

A brief physical examination will be performed at the time points specified in Section 1.3. A brief physical examination will include, at a minimum, assessments of general appearance, skin, lungs, cardiovascular system, and mental status.

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

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

8.2.2 Vital signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed as outlined in the Schedule of Activities (see Section 1.3).

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

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

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

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

8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR,

QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

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

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

8.2.4 Clinical safety laboratory assessments

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

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or at the Follow-up Visit of study medication should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or medical monitor.

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

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

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

8.2.5 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 Univerity 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. At the Screening Visit, "Baseline/Screening" version of the C-SSRS will be completed. At all other visits, "Since Last Visit" version of the C-SSRS will be completed as indicated on the Schedule of Activities (Section 1.3).

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

8.2.6 Psychiatric and mental status

Psychiatric and mental status will be assessed at Baseline and scheduled visits as specified in Section 1.3.

The psychiatric and mental status of participating subjects will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms. The parameters that will be evaluated are Psychiatric symptoms, mental impairment and behavioral problem (as 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.

8.3 Adverse events

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

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue PSL or UP0071 (see Section 7).

8.3.1 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 (Section 1.3).

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. 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 participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 1.3).

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

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

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

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

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

8.3.5 Pregnancy

Details of all pregnancies in female study participants and, if indicated, female partners of male study participants will be collected after the start of study treatment and until 30 days after the birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the study participant is lost to follow up and/or refuses to give information, written documentation of attempts to contact the study participant needs to be provided by the Investigator and filed at the site. 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 an early discontinuation visit.
- The study participant should immediately stop the intake of the study medication or be down-titrated as instructed at the early discontinuation visit.

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

8.3.6 Adverse events of special interest

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

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

8.4 Safety signal detection

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

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

8.5 Treatment of overdose

For this study, any dose of treatments (PSL, ethanol, and CBD) 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 Sponsor Medical Monitor immediately.

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

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

8.6 Pharmacokinetics

Whole blood samples will be collected for measurement of plasma concentrations of PSL, its metabolite, CBD and its active metabolite, as specified in the Schedule of Activities (Section 1.3). Urine samples will be collected for measurement of urine concentrations of PSL and/or metabolites depending on the outcome of PSL (and metabolite) PK analyses. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Ethanol breath sampling will be performed during ethanol/placebo infusion as specified in the Schedule of Activities (Section 1.3).

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 IRB/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 (or equivalent document).

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

8.7 Pharmacodynamics

All study participants will undergo at least 1 PD training session at Screening or during a separate visit for each PD assessment in order to be familiar with the test. Baseline PD assessment will be collected as a duplicate at Day 1 predose. The PD training sessions will be conducted according to the standard operating procedures at the site.

8.7.1 VAS for alcohol intoxication

The specific study participantive effects of alcohol will be assessed by VAS alcohol effects, asking the study participant to indicate the size of the alcohol effect. The scale consists of a 10cm line anchored on the left end by "sober" and on the right end by "drunk." Study participants mark a point on the line that best represents their subjective state corresponding to the condition tested. The result is a distance calculated from the mark on the line.

8.7.2 VAS feeling (Bowdle)

The Bowdle VAS (B-VAS) evaluates psychedelic effects. These could cluster into 2 distinct total sum scores "internal perception" (reflects inner feelings that do not correspond with reality, including mistrustful feelings) and "external perception" (reflects a misperception of an external stimulus or a change in the awareness of the study participant's surroundings). From the B-VAS, composite scores of "internal perception" (5 items) and "external perception" (6 items) will be calculated as described in Zuurmann et al, 2008. In addition, all 13 items could be analyzed also separately.

8.7.3 VAS according to Bond-Lader

The study participantive VASs for this study are the Bond and Lader of Mood and Alertness Scales (Bond and Lader, 1974). This VAS scale consists of 16 bipolar self-rating 100mm long lines between 2 opposite adjectives. The study participant will indicate on the line how she/he is feeling at the evaluation time. The response is scored by measuring the distance in mm between the left end of the line and the study participant's mark. This questionnaire derives 3 factors that assess change in self-rated alertness, self-rated calmness, and self-rated contentment. A computerized version of this test will be used, with the participant using the computer mouse.

8.7.4 Saccadic eye movements

Saccadic peak velocity is one of the most sensitive parameters for sedation. The use of a computer for measurement of SEM was originally described by Baloh et al, 1975. Recording of eye movements will be performed in a quiet room with ambient illumination. Recording and analysis of SEMs will be conducted with a microcomputer-based system for sampling and analysis of eye movements. A camera-based eye-tracking system will be used for monitoring eye movements towards target signals. Head movements will be restrained using a fixed head support. Saccadic eye movements will be recorded for stimulus amplitudes of approximately 15 degrees to either side. Sixteen saccades will be recorded with interstimulus intervals varying randomly. Average values of latency (reaction time), saccadic peak velocity of all correct saccades, and inaccuracy of all saccades will be used as parameters. Saccadic inaccuracy will be calculated as the absolute value of the difference between the stimulus angle and the corresponding saccade, expressed as a percentage of the stimulus angle. Saccadic eyes movements are specific measures of alertness and sedation. Peak velocity decreases and latency increases with sedation.

8.7.5 Smooth pursuit eye movements

For smooth pursuit eye movements, the target will move sinusoidally at frequencies ranging from 0.3 to 1.1Hz, by steps of 0.1Hz. The amplitude of target displacement corresponds to 22.5°eyeball rotation to both sides. Four cycles will be recorded for each stimulus frequency. The time during which the eyes are in smooth pursuit of the target will be calculated for each frequency and expressed as a percentage of stimulus duration. The average percentage of smooth pursuit for all stimulus frequencies will be used as a parameter. This parameter can be used as an accurate biomarker for oculomotor function and attention (Lehtinen et al, 1982). The method has been validated at the CHDR by Van Steveninck et al (Van Steveninck et al, 1993; Van Steveninck et al, 1989) based on the work of Bittencourt et al (Bittencourt et al, 1983) and the original description of Baloh et al (Baloh et al, 1975).

8.7.6 Adaptive tracking

The adaptive tracking test will be performed as originally described by Borland and Nicholson (Borland and Nicholson, 1984), using customized equipment and software. Adaptive tracking is a pursuit tracking task that has proved to be useful for measurement of CNS effects of alcohol, various psychoactive drugs and sleep deprivation (Van Steveninck et al, 1999; Van Steveninck et al, 1991). Each test will be preceded by a run-in period. Performance will be scored after a fixed period of 3.5 minutes and reflected visuo-motor control and vigilance. The average performance scores will be used in the analysis.

8.7.7 Body sway

Body sway will be measured by CHCR NeuroCart. Body Sway test measures the study participant's body movements in a single direction. Study participants will be asked to stand erect and motionless with their eyes closed. The amplitude and direction of any Body Sway will be recorded for 1 minute.

8.8 Genetics

Archive blood samples for genotyping of drug metabolizing enzymes will be collected as specified in the Schedule of Activities (Section 1.3).

8.9 Biomarkers

Biomarkers are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set (ES): All study participants who have signed the informed consent.
- Randomized Set (RS): All enrolled study participants who were randomized will be included in the RS.

- Full analysis Set (FAS): All randomized study participants who received IMP according to the treatment the study participants actually received.
- Pharmacokinetic Per Protocol Set (PK-PPS): PK-PPS is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PK parameters and for whom a sufficient number of samples are available to determine at least 1 PK parameter.
- Pharmacodynamic Per Protocol Set (PD-PPS): PD-PPS is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PD parameters and for whom a sufficient number of PD assessments are available to determine at least 1 PD parameter.

9.2 General statistical considerations

All 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. Categorical endpoints will be summarized using number of study participants, frequency, and percentages. Missing data will not be imputed.

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

9.3 Planned efficacy/outcome analyses

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

9.4 Planned pharmacodynamic analyses

All PD parameters (raw values, change from Baseline, and percentage change from Baseline) and variables will be listed and summarized by study part and treatment with mean, median, standard deviation (SD), minimum and maximum for the PD-PPS.

9.4.1 Ethanol and PSL (Part A)

The similarity of the PD parameters between treatments with ethanol and without ethanol (ethanol placebo alone, ethanol alone, PSL with ethanol placebo, PSL with ethanol) will be analysed separately by a mixed model of analysis of variance (ANOVA) with treatment, sequence, period, time, and treatment by time as fixed effects; with subject, subject by treatment, and subject by time as random effect; and with the (average) Baseline value as covariate. The primary comparison is PSL with ethanol vs PSL alone. The other comparisons will be: PSL alone vs ethanol placebo, ethanol alone vs ethanol placebo alone, and PSL with ethanol vs ethanol alone. Different contrasts (with estimate difference and 95% confidence interval [CI]) from ANOVA will be defined for each of these comparisons.

9.4.2 Cannabidiol and PSL (Part B)

The similarity of the PD parameters between treatment with CBD and without CBD will be analysed by a mixed model ANOVA with treatment, sequence, period, time, and treatment by time as fixed effects; with study participant, study participant by treatment, and study participant by time as random effect; and with the (average) Baseline value as covariate. Estimated

differences with 95% CI will be provided. The primary comparison is PSL with CBD vs PSL alone (from Part B Treatment Period 2). The other comparisons will be: PSL with CBD vs CBD alone.

9.5 Planned pharmacokinetic analyses

Pharmacokinetic parameters of PSL (and metabolites [redacted]) and CBD (and metabolite [7-hydroxy-CBD]) ($C_{max,ss}$, t_{max}, AUC_{τ}, $t_{½}$, $CL_{ss/F}$) will be estimated using noncompartmental analysis (NCA) with Pharsight Phoenix® WinNonlin® v6.3 (or higher) software.

Pharmacokinetic analyses will be performed using the PK-PPS set.The individual plasma concentration of PSL and metabolites, CBD and metabolites and PK parameters of CBD, PSL and metabolites will be summarized by treatment group using descriptive statistics (number of observations [n], geometric mean, lower and upper 95% CI, geometric coefficient of variation [CV], arithmetic mean, SD and CV, median, and minimum and maximum value) and graphical displays.

For the calculation of descriptive statistics, a plasma concentration below the lower limit of quantification (LLOQ) will be substituted by LLOQ/2. Mean, SD, and CV will be calculated only if at least two-thirds of the individual measurements are above or equal to LLOQ. Minimum will be reported if all measurements are above or equal to LLOQ. Individual concentration time profiles will be displayed graphically on a linear scale and semilogarithmic scale. Geometric mean profiles with lower and upper limit of the 95% CI for the linear scale and without limits for the semilogarithmic scale will be displayed.

9.5.1 Ethanol interaction on PSL (Part A)

Effects of ethanol on log-transformed PK parameters ($C_{max,ss}$, AUC_{τ}) of PSL and its metabolites will be analysed with a mixed model of variance for a 2x2 cross-over with fixed factors of treatment, sequence, period and random factor study participant within sequence. Estimation of geometric ratio of PK parameters between the 2 treatments (ethanol+PSL vs ethanol placebo+PSL) with their 90% CI will be provided.

Lack of ethanol effect on PSL will be concluded if the 90% CI of the ratio between ethanol+PSL and ethanol placebo+PSL of the least squares means for the log transformed AUC_{τ}, and $C_{max,ss}$ is within the conventional acceptance range of 80% to 125%.

9.5.2 PSL interaction on ethanol (Part A)

Individual breath ethanol concentration-time data will be listed by study participant and treatment and will be summarized by treatment (ethanol+PSL and ethanol) presenting the number of observations, geometric mean, lower and upper limit of the 95% CI for the geometric mean, geoCV(%), arithmetic mean, SD, median, minimum, and maximum.

The individual metabolizing capacity will be characterized by calculating the total ethanol dose, ie, the total amount of ethanol infused during each of the treatments.

Total ethanol dose will be analyzed by mixed model ANOVA with treatment, sequence, and period as fixed factors, and study participant within sequence as a random factor to assess potential differences of metabolizing capacity between treatments (with and without PSL). The

ratio of the least squares means in ethanol dose between treatment with PSL and treatment without PSL, and its 90% CI will be calculated.

9.5.3 Cannabidiol interaction on PSL (Part B)

Effects of CBD on log-transformed PK parameters ($C_{max,ss}$, AUC_{τ}) of PSL and its metabolites will be analysed with a mixed model of variance for a 2x2 cross-over with fixed factors of treatment, sequence, period and random factor study participant within sequence. Estimation of geometric ratio of PK parameters between the 2 treatments (CBD+PSL vs PSL) with their 90% CI will be provided. The PK of PSL without CBD is obtained in Part B Treatment Period 2.

9.5.4 PSL interaction on CBD (Part B):

Effects of PSL on log-transformed PK parameters ($C_{max,ss}$, AUC_{τ}) of CBD and its metabolites will be analysed with a mixed model of variance for a 2x2 cross-over with fixed factors of treatment, sequence, period and random factor study participant within sequence. Estimation of geometric ratio of PK parameters between the 2 treatments (PSL+CBD vs PSL placebo+CBD) with their 90% CI will be provided.

9.6 Planned safety analyses

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

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment and treatment-emergent according to the intake of the IMP. All AE data will be listed by study participant number, visit, treatment and time. The listings will include the following data pertaining to the AEs: start and end dates with relative days to study medication administration, duration, intensity, seriousness, relationship to study medication, action taken, and final outcome.

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

Safety laboratory measurements, vital signs and 12-lead ECGs parameters will be tabulated by study part and treatment 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 examinations abnormalities and psychological and mental status abnormalities will be listed.

9.7 Handling of protocol deviations

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

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

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

9.8 Handling of dropouts or missing data

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

9.9 Planned interim analysis and data monitoring

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

9.10 Determination of sample size

Based on the study PK and PD objectives, the total planned number of healthy study participants will be 44, including 22 evaluable participants for Part A and 22 evaluable participants for Part B.

For Part A, the sample size is based on pragmatic considerations and the ability to detect an ethanol effect on PD assessments (CNS variable). A sample size of 22 evaluable study participants provides 80% power to detect an ethanol effect in a difference in means of 3.96 (% points) for the smooth pursuit test, which is the most sensitive CNS variable to ethanol effects, assuming a SD of difference of 6.0 (% points) based on previous ethanol clamp interaction studies and using a paired t-test 2-sided with a 0.05 significance level. This sample size is also valid for the CBD effect assessment (Part B).

For Part B, a sample size of 22 evaluable study participants is needed to assess the PK interaction between PSL and CBD, and to estimate the mean PSL AUC_τ ratio of with/without CBD of 1.5 with a half-width of the CI of 0.3. This sample size has been evaluated with a conditional probability of 90%, assuming an inter-participant coefficient of variation of 45% of PSL AUC_τ (observed in study UP0057), correlation of 0.5, 2-sided and $\alpha = 0.05$. A sufficient number of healthy study participants (up to 20) will be selected to have 16 completed study participants.

Regarding the assessment of the single dose formulation of CBD (under fasted conditions) in Part B (study formulation vs Epidiolex formulation from literature data), 16 healthy study participants are required to assess the similarity of the 2 formulations (equivalence range of 50 to 200% based on the high variability of CBD) with a 80% power and assuming an expected geometric mean ratio of AUC and C_{max} between 0.8 and 1.3, and inter-participant CV of 80% (based on CBD literature) and correlation of 0.5.

Sample size computations were performed using SAS version 9.4 (Proc Power).

Drop outs will be replaced at the discretion of the Investigator and Sponsor.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and eithical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, 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, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

As part of the IRB/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 participant risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

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

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

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

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

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

10.1.4 Data protection

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

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

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

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

10.1.5 Committees structure

Not applicable.

10.1.6 Data quality assurance

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of 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 participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

10.1.8 Study and site closure

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

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

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

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

10.1.9 Publication policy

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

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the 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[1]	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1,2]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin (direct is only measured if total >1xULN)
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting at Screening)	Calcium	Alkaline phosphatase	
Routine Urinalysis[1]	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.			
Other Screening Tests	• Follicle-stimulating hormone (at Screening only to confirm postmenopausal status in female study participants • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Breath alcohol test			

Laboratory Assessments	Parameters
	• Pregnacy test: Urine or serum beta human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential; serum hCG test used at Screening only) • Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab)

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

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

Investigators must document their review of each laboratory safety report.

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

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

10.3.1 Definition of AE

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

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

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

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

10.3.2 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic

bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and follow up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 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 1 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

Reporting of SAEs

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

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

10.4.1.1 Woman of childbearing potential

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

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception guidance

10.4.2.1 Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the treatment period and for at least 7 days after the last dose of study treatment as described in Section 5.1:

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

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

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

10.4.2.2 Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Urine beta HCG pregnancy testing, with a sensitivity of 10mIU/mL will be performed according to the schedule of activities (Section 1.3).

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 consistently and correctly use a highly effective method of contraception as described in Table 10-1.

Table 10-1: Highly Effective Contraceptive Methods

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

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

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

10.4.2.3.2 Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of the pregnancy will be

reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.2.3.3 Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the sponsor as described in Section 8.3.5. 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 DNA sample will be taken for future exploratory purposes to caracterize outlier PK profile (CYP ADME purpose).

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

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

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

Study participants with potential drug-induced liver injury should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or 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 >5xULN. 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 a SAE data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). MONITORING: If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:	• 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

• 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.	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF. If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week.) 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 CRFs.

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

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

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

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

Not applicable.

10.8 Appendix 8: Rapid Alert Procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

ADE	adverse device effect
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
app	application
ASADE	anticipated serious adverse device effect
AST	aspartate aminotransferase
BMI	body mass index
BZDs	benzodiazepines
cBZR	central benzodiazepine receptor
CBD	cannabidiol
CDMS	clinical data management system
CNS	central nervous system
CI	confidence interval
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CV	coefficient of variation
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EDC	electronic data capture
EEG	electroencephalogram
EMA/EMEA	European Medicines Agency
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full analysis Set
FDA	Food and Drug Administration

$GABA_A$	gamma-aminobutyric acid type A
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine devices
IUS	intrauterine systems
LEV	levetiracetam
NCA	non-compartmental analysis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OTC	over-the-counter
PD	pharmacodynamics(s)
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per Protocol Set
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PR	pulse rate
PS	Patient Safety
PSL	Padsevonil
RMF	medical device risk management file
RNA	ribonucleic acid
RR	respiratory rate
RS	Randomized Set

SADE	serious adverse device effect
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reactions
SV2	synaptic vesicle protein 2
TMF	trial master file
UADE	unanticipated adverse device effect
ULN	upper limit of normal
USADE	unanticipated serious adverse device effect

10.11 Appendix 11: Protocol amendment history

Not applicable.

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SPONSOR DECLARATION

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

Approval Signatures

Name: up0071-protocol-amend-1

Version: 1.0

Document Number: CLIN-000137909

Title: UP0071 Protocol Amendment 1

Approved Date: 25 Jul 2019

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 25-Jul-2019 14:10:45 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 25-Jul-2019 14:13:45 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 25-Jul-2019 15:55:31 GMT+0000