STATISTICAL ANALYSIS PLAN

Study: UP0035

Product: Padsevonil

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

SAP/Amendment Number	Date
Version 1.0	28-May-2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
ALT	alanine aminotransferase
ALQ	above the limit of quantification
ANOVA	analysis of variance
AST	aspartate aminotransferase
ASP	all study participants
AUC	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to the last quantifiable concentration
AUC_{0-12}	area under the curve from time 0 to 12h
$AUC\tau$	area under the curve over a dosing interval
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BP	Blood pressure
CI	confidence interval
CL/F	apparent total clearance
CL_{SS}/F	apparent total clearance at steady-state
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration at steady-state
C_{min}	minimum observed plasma concentration
CRF	case report form
CRU	clinical research unit
C_{trough}	plasma trough concentration

CSR	clinical study report
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
DEM	data evaluation meeting
DDI	Drug Drug Interaction
ECG	electrocardiogram
EDV	Early Discontinuation Visit
EE	Ethinylestradiol
EOS	End of Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
geoCV	geometric coefficient of variation
ICF	Informed Consent form
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IPD	important protocol deviation
LLOQ	lower limit of quantification
LN	Levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
$MR_{AUC\tau}$	Metabolic ratio for AUCτ
$MR_{Cmax,ss}$	Metabolic ratio for $C_{max,ss}$
n	number of study participants number of available observations
NCA	Noncompartmental analysis
OC	Oral contraceptive

PDILI	Potential drug-induced liver injury
PKS	Pharmacokinetic Set
PK	Pharmacokinetic(s)
PK-PPS	Pharmacokinetic-Per Protocol Set
PR	pulse rate
PSL	Padsevonil
PT	preferred term
QTcF	QT corrected for heart rate using Fridericia's formula
RR	respiratory rate
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	single dosing
sd	standard deviation
SFU	Safety Follow-up
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFLs	tables, figures and listings
t_{max}	time to maximum concentration (C_{max} or $C_{max,ss}$)
$t_{1/2}$	terminal elimination half-life
$t_{1/2,ss}$	terminal elimination half-life at steady state
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of UP0035. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

This SAP is based on the following documents:

- Original Clinical Study Protocol dated 01 Aug 2019
- Clinical Study Protocol Amendment 1 dated 10 Oct 2019
- File Note with number Ward v3 (HMR code 19-009) dated 12 Dec 2019
- Clinical Study Protocol Amendment 2 dated 25 Feb 2020

Unless specified in the sections below, the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. In addition, if analysis definitions must be modified or updated prior to database lock, a SAP amendment will be required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale.

Following UCB's decision to terminate the padsevonil (PSL) epilepsy project in partial onset seizures, the UP0035 study has been stopped and no study participants will enter study Part 2. Consequently, study results reporting will be restricted to study Part 1 of this SAP and a subset of the tables, figures, and listings will be reported in line with Clinical Trial Reporting duties (EUDRA-CT, ClinicalTrials.gov).

The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (Phillips et al, 2003).

UCB is the Sponsor and ICON PLC is the Contract Research Organization for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives and endpoints

Table 2-1: Objectives and endpoints

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

Table 2-1: Objectives and endpoints

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

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

2.2 Study design and conduct

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

Prior to Protocol Amendment 2, the intention was to screen a sufficient number of study participants to ensure that 20 study participants would be included in each treatment sequence

shown in Table 2-2. This pair of treatment sequences has now been designated as Part 1, necessitated by the introduction of a new pair of treatment sequences at the new, lower dose level, termed Part 2, for new study participants that will be enrolled under the amended protocol. At the time of Amendment 2, 14 study participants completed Part 1 and were dosed with PSL 400mg BID (7 study participants in Sequence A and 7 study participants in Sequence B). In Part 2, a sufficient number of study participants will be screened to ensure that 13 study participants are included in each treatment sequence.

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

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

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

Forty (40) evaluable study participants will be enrolled overall. A total of 14 evaluable study participants (7 study participants in each sequence) have completed Part 1 with PSL 400mg BID dosing. For Part 2 with PSL 200mg BID dosing, a total of 26 evaluable study participants are planned (13 study participants in each sequence). Study participants who are withdrawn may be replaced following discussion between the Investigator and Sponsor.

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

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

Table 2-2: Part 1 treatment sequences

Part 1 Treatment Sequence A

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

Part 1 Treatment Sequence B

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

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

Table 2-3: Part 2 treatment sequences

Part 2 Treatment Sequence A

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

Part 2 Treatment Sequence B

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

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

Table 2-4: Schedule of activities- Part 1 Treatment Sequence A

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

Table 2-4: Schedule of activities- Part 1 Treatment Sequence A

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

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

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

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

[c] At Screening, Baseline (Day -1), Day 6, and Day 12, a full physical examination will be performed. On all other days a physical examination is performed, it will be a brief physical examination. On Days 7 to 11, physical examination will not be performed.

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

[e] ECG will be completed on Days 2, 4, 6, and 12 only of multiple day periods during Treatment Sequence A.

[f] During the OC+PSL Treatment Period, trough levels of PSL will be collected on morning before PSL dosing on Day 2, Day 4, Day 6, Day 8 and Day 10. Additional blood sampling for PK analysis will be taken on Day 12 (PSL PK) before (predose) and after PSL morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h postdose and on Day 13 (PSL and OC PK) before (predose) and after the PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (before morning PSL dose on Day 14), and 48h (before morning PSL dose on Day 15) postdose.

[g] During OC+PSL Treatment Period, blood sampling for OC PK analysis will be taken on Day 13 (before OC+PSL morning dose) and after PSL and OC morning dose at 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 14), 36h (Day 14), and 48h (Day 15) postdose. During the single-dose OC period, PK blood samples will be taken on Day 34 at predose and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h (Day 35), 36h (Day 35), and 48h (Day 36) postdose.

[h] Mitra ™ (finger prick) blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 12 only for selected study participants.

[i] The study participant can be discharged on Day 20 or Day 21, at the discretion of the principal investigator.

Table 2-5: Schedule of activities- Part 1 Treatment Sequence B

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

syphilis, and HCV-Ab)																
12-lead ECG	X	X	X				X	X[e]	X[e]	X[e]	X	X			X	X
Urine and cotinine drug screen, and alcohol breath test	X	X				X (D17)										
Recording of adverse events/medical procedures	X	X	X	X	X	X (D17)	X	X	X	X	X	X	X	X	X	X
Blood sampling for genotyping of drug metabolizing enzymes and/or transporters		X														
Admit to clinic		X				X (D17)										
Administer PSL							X	X	X	X	X	X	X	X	X	
Administer OC			X								X					
Blood sampling for PSL PK levels[f]								X[f]	X[f]	X[f]	X[f]	X[f]	X[f]			
Blood sampling for OC PK levels[g]			X[g]	X[g]	X[g]						X[g]	X[g]	X[g]			
Blood sampling for cross-validation[h]										X						
Discharge					X											X (D37 or D38)[i]

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

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

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

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

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

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

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

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

[h] Mitra ™ (finger prick) blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 29 only.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[j] Mitra ™ (finger prick) and venous blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 8 only for selected study participants. See Section **Error! Reference source not found.** for details about selection.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[j] Mitra ™ (finger prick) and venous blood samples will be taken at 0.5h, 1h, 3h, 6h, 12h postdose on Day 25 only for selected study participants. See Section **Error! Reference source not found.** for details about selection.

2.3 Determination of sample size

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

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

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

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

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by ICON PLC and supervised by UCB. The datasets will follow the UCB analysis data model (ADaM) data specifications. All statistical analyses will be performed using SAS® Version 9.4 or later (SAS Institute, Cary, NC, USA).

Pharmacokinetic parameters will be determined by non-compartmental analysis (NCA) with Pharsight Phoenix® WinNonlin® Build 8.0 or higher (Certara L.P., Princeton, NJ, NCA) software. Pharmacokinetic analyses will be performed and reported for each study part. PK parameter estimation will use actual doses administered and the actual sampling times relative to time of dose administration.

Categorical endpoints will be summarized using number of study participants (n), frequency, and percentages. Missing data will not be imputed. Individual plasma concentrations and PK parameters will be presented using 3 significant digits.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all study participants fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed
- All other percentage displays will use 1 decimal place

Percentages displayed based on continuous data (e.g. percentage changes from baseline) will be displayed to 1 decimal place. Unless otherwise stated, the denominator for the percentages will be based on the number of study participants in the respective analysis set.

Continuous variables will be summarized by day and time point (where applicable) including number of study participants (n), mean, median, standard deviation (sd), minimum and maximum. Geometric coefficient of variation (geoCV), geometric mean and 95% confidence interval (CI) for the geometric mean will also be presented in the descriptive statistics for the plasma concentrations and PK parameters for EE, LN, PSL and its metabolites ([redacted] [redacted] and [redacted]). In all outputs, the confidence limits will be restricted to the possible values that the variable can take.

Venous plasma samples will be obtained for EE, LN, PSL and its metabolites.

When reporting descriptive statistics, the following rules will apply in general except for PK concentration data (plasma and blood (PK) of EE, LN, PSL and its metabolites ([redacted] and [redacted]):

- n will be an integer
- Mean (arithmetic and geometric), standard deviation and median will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the original data
- Confidence intervals will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the value around which the confidence interval is constructed
- Coefficient of variation (CV) will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value
- If no study participants have data at a given time point, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be left blank.

When reporting individual values and descriptive statistics for PK concentration data (EE, NL, PSL and its metabolites ([redacted] and [redacted]), the following rules will apply regarding rounding and precision:

- Individual values for PK concentration data will be reported to the same level of precision as received from the bioanalytical laboratory
- Descriptive statistics for PK concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure– depending on the reporting format of the original data with a maximum of 3 significant digits - for the mean (arithmetic and geometric), median and standard deviation. The 95% CI for the geometric mean will use 1 decimal place more, or 1

significant figure more – depending on the reporting format of the original data – than the value around which the confidence interval is constructed

- Geometric CV will be reported as a percentage to 1 decimal place

When reporting individual values and descriptive statistics for PK parameters (PK of EE, LN, PSL and its metabolites ([redacted] and [redacted])) the following rules will apply with regard to rounding and precision:

- Individual values for PK parameters will be reported to 3 significant figures
- Descriptive statistics for PK parameters should be rounded to 4 significant figures for the mean, median and standard deviation and to 3 for the others

Data listings containing all documented data and all derived data will be generated and presented by treatment sequence (treatment sequence A and treatment sequence B) and treatment period.

3.2 General study level definitions

3.2.1 Relative day

Relative day will be calculated based on the treatment received. Therefore, three relative days are defined, based on treatment with OC alone, PSL alone and the combination of OC and PSL.

The relative day of an event will be derived with the date of first dose of the treatment, as reference. For Padsevonil, this will be Day 1 in Sequence A and Day 18 in Sequence B. For OC alone this will be Day 34 in Sequence A and Day 1 in Sequence B. For the combination of PSL+OC the first dose is given on Day 13 in Sequence A and Day 30 in Sequence B

Relative days for an event or measurement occurring before the date of first dose of treatment are calculated as follows:

$$Relative\ Day = Event\ Date - Date\ of\ First\ Dose\ of\ Treatment$$

The relative day for an event or measurement occurring on the date of first treatment dose is 1. The relative day for an event or measurement occurring on or after the date of first treatment dose to the date of the last dose will be calculated as follows:

$$Relative\ Day = (Event\ Date - Date\ of\ First\ Dose\ of\ Treatment\ ) + 1$$

For events or measurements occurring after the date of last treatment dose, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

$$Relative\ Day = +\ (Event\ Date - Date\ of\ Last\ Dose\ of\ Treatment\ )$$

There is no relative Day 0. Relative day will not be calculated for partial dates in cases where relative day is shown in a study participant data listing. In such cases, relative day should be presented as '--' in the relevant study participant data listing.

3.2.2 Study periods

For each study participant completing Part 1, the expected maximum duration of participation will be approximately 75 days with a maximum of 20 days exposure to investigational product (19 days exposed to PSL, (with or without OC) and one day exposed to OC only).

For each study participant completing Part 2, the expected maximum duration of participation is approximately 70 days with a maximum of 12 days exposure to investigational product (11 days exposed to PSL, (with or without OC) and one day exposed to OC only).

The various periods of the study are described below:

- Screening/Baseline Period (Day -28 to Day -1)

  The Screening Period consists of a single Screening Visit, which will be conducted at the unit within 28 days prior to check-in for treatment period, and a Baseline Visit, which will be conducted at HMR, the clinical research unit (CRU) 1 day prior to treatment period (on Day -1). Study participants will check-in at the CRU on Day -1.

  Part 1

  Sequence A (Day 1 to Day 36)

  In Part 1, study participants enrolled in Treatment Sequence A will be administered PSL BID (up-titration to steady-state [400mg BID]) from Day 1 to Day 5, followed by a maintenance period from Day 6 to Day 12 with a single dose of OC administered on the morning of Day 13. A taper of PSL will occur from Day 15 to Day 19. Starting on Day 20, the study participants will then complete a 14-day Washout Period followed by a return to the clinic for the OC-only dosing on Day 34. A SFU Visit will occur between Day 41 and Day 44.

  Treatment Sequence A consists of the "PSL+OC Period" followed by the "OC alone Period".

  Sequence B (Day 1 to Day 36)

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

  Treatment Sequence B consists of the "OC alone Period" followed by the "PSL+OC Period".

  Part 2

  Sequence A (Day 1 to Day 28)

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

  Treatment Sequence A consists of the "PSL+OC Period" followed by the "OC alone Period".

Sequence B (Day 1 to Day 28)

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

Treatment Sequence B consists of the "OC alone Period" followed by the "PSL+OC Period".

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

3.3 Definition of Baseline values

In either study part, Baseline will be the last non-missing value prior to first dosing on Day 1 (PSL dosing in Treatment Sequence A or OC dosing in Treatment Sequence B). Scheduled or unscheduled measurements can be used as the Baseline value.

If a measurement is repeated at Baseline and is obtained prior to dosing, then the last available measurement will be used as the Baseline value. If an assessment occurs on the date of dosing, the time must occur prior to the time of dosing.

Variable	Baseline definition
Hematology, serum, chemistry, urinalysis	The baseline value is defined as the value on Day -1. If the baseline value is missing, the value obtained at Screening will be used.
Vital signs	The baseline value is defined as the last value prior to dosing.
ECG	12-lead ECG will be measured in triplicate. Baseline is the mean of the last three available measurements prior to dosing. If less than three replicates are available, the mean of the available replicates at the same visit (prior to dosing) will be considered as baseline.
C-SSRS	The baseline value is defined as the value from Day -1. If the baseline value is missing, the value obtained at Screening will be used.

The change from Baseline to any subsequent post-Baseline visit will be calculated as the simple difference between that post-Baseline visit's value and the Baseline visit value, as below:

$$Change\ from\ Baseline = Post\ Baseline\ Visit\ Value\ - Baseline\ Visit\ Value$$

3.4 Protocol deviations

Important protocol deviations (IPD) are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual study participant. Study participants will be excluded from SS only when there is documented evidence that they received no treatment. Study participants may be excluded from the Pharmacokinetic Set (PKS) if they had an important protocol deviation affecting the PK parameters.

The criteria for identifying protocol deviations and the classification of protocol deviations will be captured in the Important Protocol Deviations document. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all study participants.

Important protocol deviations will be reviewed as part of an ongoing data cleaning process prior to database lock to confirm exclusion from analysis sets. After all data have been verified/coded/entered into a database, a data evaluation meeting (DEM) will be held.

At least one DEM will be performed at the following time:

- Prior to the final analysis after all data have been verified/coded/entered into the database

Additional DEMs may be conducted as deemed necessary.

The purpose of these DEM reviews will be to review all protocol deviations, determine whether the deviations are considered important or not important, define the analysis sets, and check the quality of the data. The reviews will also help decide how to manage problems in the study participants' data (e.g., missing values, withdrawals and protocol deviations).

Accepted deviations from scheduled time points will be described in the appropriate documents and included in the Study Master File. After the pre-analysis review, resolution of all issues, and documentation of all decisions (including inclusion into each of the analysis sets) at the final DEM, the database will be locked.

3.5 Analysis sets

3.5.1 All Study Participants

All Study Participants consists of all study participants who have signed the Informed Consent Form (ICF).

3.5.2 Safety Set (SS)

The Safety Set (SS) consists of all study participants who received at least one dose of study medication (PSL or OC).

3.5.3 Pharmacokinetic Set (PKS)

The Pharmacokinetic Set (PKS) is a subset of the SS, consisting of those study participants who had no important protocol deviations affecting the PK parameters of EE, LN, or PSL and its metabolites and for whom at least one measurable concentration exists.

3.6 Treatment assignment

It is expected that study participants will receive treatments as per the randomized treatment sequence and hence the analyses will be based on the randomized treatment. If a study participant was randomized but not dosed in any treatment period, the study participant results will be reported under the randomized treatment group. For safety analyses based on the SS, study participants will be classified according to the medication that was actually received.

Except for PK, concomitant medications, and adverse events, tables will be presented separately for each study part by randomized Treatment Sequence (Sequence A: PSL+ OC followed by OC alone and Sequence B: OC alone followed by PSL+OC) and overall. Listings will be presented by study part, randomized treatment sequence, and study participant number. PK summaries will be presented by study part, treatment period (OC alone and OC+PSL), and analyte (EE, LN; PSL and its metabolites). Concomitant medication and adverse event tables will be presented separately for each study part by treatment (OC alone, PSL alone, and OC+PSL).

A detailed schematic diagram of the study is provided in Table 2-2 and Table 2-3.

3.7 Center pooling strategy

The data will come from one center. The statistical analyses will not be performed by center.

3.8 Coding dictionaries

Adverse events and medical history will be coded using version 22.0 of the Medical Dictionary for Regulatory Activities (MedDRA®). Medications will be coded according to the latest version of the World Health Organization Drug Dictionary (WHODD) (Version SEP/2017). Medical procedures will not be coded.

The versions of the coding dictionaries used will be displayed in the relevant TFLs.

3.9 Changes to protocol-defined analyses

- Changes in the name of analysis datasets (section 9.1 of the protocol):

  - The analysis set "Enrolled set" will be renamed as "All Study Participants" in the SAP and will correspond to all study participants who sign the informed consent form.

  - The analysis set "Pharmacokinetic Per Protocol Set (PK-PPS)" will be renamed as "Pharmacokinetic Set (PK Set)" in the SAP and will still correspond to the protocol definition of PK-PPS.

- For the purpose of the analysis of concomitant medications and adverse events 3 groups will be created, based on the treatment administered. The results will be presented for PSL alone, OC alone and the combination of PSL and OC.
- For the primary PK analysis, ping-pong plots have been added for EE and LN for C_{max}, and AUC for OC with and without PSL.
- Ping-pong plots have also been added for $C_{max,ss}$ and AUC_{τ}, for PSL and its two metabolites ([redacted] and [redacted]) for PSL with and without OC.
- Ping-pong plots have been added for $C_{max,ss}$, AUCτ, $MR_{AUC\tau}$, $MR_{Cmax,ss}$, CL_{ss}, $t_{1/2}$, for PSL (with and without OC).
- Furthermore, the relationship between MR and Cmax (with and without PSL) of EE and LN, and the exposure to PSL (AUCτ) will be explored.
- Ctrough and MR based on AUCτ of PSL and its two metabolites, will also be compared between days (with OC [Day 13 for Sequence A and Day 30 for Sequence B] and without OC [Day 12 for Treatment Sequence A and Day 29 for Treatment Sequence B] using analysis of variance on the log-transformed parameters and estimation of geometric ratio of PK parameters between days with their 90% CI will be provided.
- Furthermore, the relationship between individual C_{max} (with and without PSL) of EE and LN and the exposure to PSL (AUC_{τ}) will be assessed by scatterplots and linear regression analyses.
- According to the protocol, the occurrence and incidence of AEs will be summarized by treatment sequence according to the intake of PSL (pretreatment or treatment-emergent) and

by intensity or relationship to PSL. As the relationship to PSL alone is not documented in the CRF, the relationship to study medication (PSL, PSL+OC, and OC) will be analyzed. Consequently, the definition of TEAE will be related to treatment (PSL, PSL+OC, or OC) and a TEAE will be attributed to a treatment according to the start date.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

In general, there will be no imputation of missing data unless otherwise stated below.

Missing data will be handled as described in the sections below for safety laboratory and PK results. No other imputations will be performed.

4.2.1 Pharmacokinetics

The 95% CI lower and 95% CI upper should be left blank if the standard deviation (or equivalently, the geometric CV) is 0. Measurements of PK concentrations that are below the limit of quantification (BLQ) and which are occurring prior to t_{max} will be imputed with half of the lower limit of quantification (LLOQ/2), except for embedded BLQ values (between two measurable data points) which will be treated as missing, for the purpose of calculating the geometric mean and its 95% CI, the geometric CV, the arithmetic mean and standard deviation for summaries and figures. Post-t_{max}, BLQ values will be treated as missing. Descriptive statistics of concentrations will be calculated if at least $2/3^{rd}$ of the individual data points are quantifiable (≥LLOQ).

For all individual PK concentration figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements which will be imputed with zero (to capture lag-time) for linear scale plots.

The following rules will apply for PK data listings:

- Values below the LLOQ will be reported as "(BLQ)" in the listings

The following rules will apply for PK summaries

- Descriptive statistics of plasma concentrations will be calculated if more than $2/3^{rd}$ of individual data points are quantifiable (>=LLOQ) at the given time-point. However, if n<3, then only n, minimum and maximum will be presented, and the median will also be presented if n=3. The other descriptive statistics will be left blank.
- For $t_{max,}$only N, median, minimum and maximum will be displayed into the summary statistics,
- For plasma concentration summaries, all BLQ values will be replaced by "LLOQ/2" and missing values will be excluded.

- When the mean value includes one or more replaced BLQ values then a footnote will be included to say "contains one or more BLQ value replaced by half the LLOQ value".
- For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements which will be imputed with zero for linear scale plots.
- If no study participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- The geometric CV will be calculated using the following formula where SD_{log} is the standard deviation from the log-transformed data:

$$Geometric\ CV\ (\%) = sqrt[(exp\ (SD_{log}\text{^}2) - 1)] \times 100$$

The PK analysis will be performed in accordance to the Guideline on performing NCA analysis dated 08 Nov 2017, and BLQ values will be treated as stated in this document for the NCA analysis.

4.2.2 Safety laboratory data

The rules for handling values that are BLQ or above the limit of quantification (ALQ) in the safety laboratory data will be the same as those described for PK data in Section 4.2.1.

4.2.3 Electrocardiogram data

For the 12-lead ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each time point. In the event that there are not three available measurements at a given time point, the mean will be calculated based on the number of measurements for which data are provided.

4.2.4 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as prior or concomitant

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial start dates:

- If only the month and year are specified and the month and year of the first dose of study medication is not the same as the month and year of the start date then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00h
- If only the month and year are specified and the month and year of the first dose of study medication is the same as the month and year of the start date, then the date of the first dose of study medication will be used. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of screening if this is later (if the

latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of dosing then time will be imputed as the start time of the dosing (i.e., event will be regarded as treatment-emergent)

- If only the year is specified, and the year of the first dose of study medication is not the same as the year of the start date then January 01 will be used. If time is missing this will be imputed as 00:00h
- If only the year is specified, and the year of the first dose of study medication is the same as the year of the start date, then the date of the first dose of study medication will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of screening if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of first dose of study medication then time will be imputed as the start time of the study medication intake (i.e., event will be regarded as treatment-emergent)

The following rules will be applied to partial stop dates:

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31 of the known year
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing dates and/or times will be imputed as described in Table 4-1 . Calculation rules for duration of adverse events can be found in Table 4-1 and will be applied for the calculation of duration of each AE. Adverse event duration is computed in and reported in day and time format: xx d hh:mm.

Table 4-1: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a study participant in the SS, D0 and T0 are the date and time of first administration of study medication and for screen failures, D0 is the date of the screening visit and T0 = 00:00h

Table 4-1: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
End day and time missing	D1/T1	--/--	If the stop date is missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date is missing, duration will not be calculated.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of study medication the latest value (which may be scheduled or unscheduled) will be used in the calculation of the descriptive statistics
- For repeated measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of study medication
- Unscheduled and repeated measurements will not be used in the descriptive statistics at time points after first dose of study medication
- Unscheduled measurements performed for the End of Study/Safety-Follow-Up/Early Discontinuation Visit (EOS/SFU/EDV) visit will be assigned to the EOS/SFU/EDV Visit (Section 4.4) and analyzed accordingly as an EOS/SFU/EDV Visit.

4.4 Handling of measurements obtained at the early withdrawal visit

Study participants who withdraw early from the study for any reason, including those withdrawn from study medication, will be asked to return for the EOS/SFU/EDV Visit as soon as possible after the last dose of study medication.

4.5 Interim analyses and data monitoring

Not applicable.

4.6 Multicenter studies

This study is planned to be conducted at one site. Thus, there is no plan to explore sites effect in the analysis.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of study participants

Not applicable.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

Not applicable

5 STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

The number of study participants who signed the informed consent and study participants who were screen failures, completed or prematurely discontinued the study, as well as the reason for discontinuation will be summarized separately per study part for all study participants, based on the ASP. A study participant who completed the study is defined as a study participant who completed all visits up to and including the EOS/SFU/EDV visit. If there is more than one termination due to AE, then an additional table summarizing the discontinuations due to AE will be produced. In case that only one subject discontinues due to AE, then this will be presented in a listing. The number of study participants screened, number of screen failures and primary reason for screen failure will be summarized based on the ASP.

The number and percentage of study participants included in each of the analysis sets will be summarized based on All Study Participants. Percentages will be calculated based on All Study Participants for the purpose of this summary.

In addition, the following listings will be presented:

- Study participant disposition (All Study Participants) - including screening failure reasons
- Study participant analysis sets (All Study Participants)

The listing of study participant disposition will include the date of informed consent, the date of randomization, date and time of first and last dose of PSL, date and time of first and second dose of OC, date of premature termination and primary reason (if applicable).

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types in the IPD document (see also section 3.4). A listing of all IPDs identified at the DEM will be presented by study part and treatment sequence for all study participants based on the SS and will include the deviation type and description.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-study participant listing of demographics will be presented by study part, treatment sequence (Sequence A, Sequence B) based on All Study Participants. This will include the year of birth, age (in years), sex, race, ethnicity, country, height (in cm), weight (in kg) body mass

index (BMI, in kg/m^2). The body weight will be the measurement obtained at Screening. Body mass index (kg/m^2) is documented in the CRF.

All demographic characteristics (except for year of birth) will be summarized separately for each study part by treatment sequence and overall (Sequence A, Sequence B and All Study Participants) based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years
- 19 to <65 years
- ≥65 years

Characteristics about childbearing potential and method of birth control will be listed by study part and treatment sequence for study participants in the ASP.

6.2 Other Baseline characteristics

Lifestyle characteristics including data regarding alcohol, caffeine, and tobacco use will be listed.

6.3 Medical history, procedure history and concomitant medical procedures

Medical history will be listed (by study part) and summarized (in separate incidence tables per study part) for the SS, by MedDRA system organ class (SOC) and preferred term (PT) per treatment sequence and overall. The reported term will be included in the listing. The summary will include the number and percentage of study participants, and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the 'All Participants' column.

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the date of first dose of IMP. Concomitant medications are medications taken after the first dose of IMP (PSL or OC). Concomitant medications will be attributed to the treatment in which they start. Thus, for study participants in Part 1 randomized in Sequence A, any medication taken on Day 1 through Day 13 (prior to OC intake) will be attributed to the PSL alone period; any medications taken on Day 13 (after OC intake) through Day 34 (prior to OC intake) will be attributed to the PSL+OC period and any medication taken on Day 34 (after OC intake) through Day 44 will be attributed to OC alone. For study participants in Part 1 randomized in Sequence B, any medication taken on Day 1

through Day 18 (prior to PSL intake) will be attributed to OC alone; any medications taken on Day 18 (after PSL intake) through Day 30 (prior to OC intake) will be attributed to PSL and any medication taken on Day 30 (after OC intake) through Day 46 will be attributed to PSL+OC. For study participants in Part 2 randomized in Sequence A, any medication taken on Day 1 through Day 9 (prior to OC intake) will be attributed to the PSL alone period; any medications taken on Day 9 (after OC intake) through Day 26 (prior to OC intake) will be attributed to the PSL+OC period and any medication taken on Day 26 (after OC intake) through Day 40 will be attributed to OC alone. For study participants in Part 2 randomized in Sequence B, any medication taken on Day 1 through Day 18 (prior to PSL intake) will be attributed to OC alone; any medications taken on Day 18 (after PSL intake) through Day 26 (prior to OC intake) will be attributed to PSL and any medication taken on Day 26 (after OC intake) through Day 42 will be attributed to PSL+OC.

A schematic summary is given below:

Study Part	Sequence	PSL alone	PSL + OC	OC alone
1	A	Day 1 – 13 (prior to OC intake)	Day 13 (after OC intake) – 34 (prior to OC alone intake)	Day 34 (after OC intake) - 44
	B	Day 18 (after PSL intake) – Day 30 (prior to OC intake)	Day 30 (after OC intake) - 46	Day 1 – 18 (prior to PSL intake)
2	A	Day 1 – 9 (prior to OC intake)	Day 9 (after OC intake) – 26 (prior to OC intake)	Day 26 (after OC intake) - 40
	B	Day 18 (after PSL intake) – 26 (prior to OC intake)	Day 26 (after OC intake) – 42	Day 1 – 18 (prior to PSL intake)

If a medication started prior to IMP administration (PSL or OC) and stopped after the first IMP administration (PSL or OC) or stopped during the first treatment period (for Sequence A: PSL period; for Sequence B: OC alone period), then that medication will be classified as both prior and concomitant for PSL alone or OC alone period respectively (depending on the randomized sequence).

If a medication starts prior to IMP administration (PSL or OC) and is stopped during the second treatment period (for Sequence A: PSL+OC period; for Sequence B: PSL period), then that medication will be classified as prior and concomitant for both treatment periods (PSL+OC and PSL alone). The same rule will apply for the third treatment period.

Any medications with missing dates and/or times will be handled as described in Section 4.2.4 to classify them as prior or concomitant.

Prior and concomitant medications will be listed by study part for all study participants in the SS. Prior and concomitant medication will be tabulated separately. The summary will be presented by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Tabulation for prior medications will be presented separately for each study part by treatment sequence; tabulation for concomitant medications (PSL+OC concomitant, PSL alone-concomitant and OC alone-concomitant) will be summarized separately for each study part by treatment separately for each treatment sequence.

The prior medication tabulation will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Participants' column. The concomitant medication tabulation will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the PSL+OC column.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Administration of study medication will be performed under the supervision of the Investigator (or designee). Compliance will be monitored by drug accountability. A Drug Accountability form will be used to record study medication dispensing and return information on a by-study participant basis. Drug administration/consumption will be recorded and any discrepancies with the dosing regimen will be explained. Dosing deviations will be included in the listing of IPDs where applicable.

No formal calculations of compliance will be presented as all study medication is administered on site.

8 EFFICACY ANALYSES

Not applicable.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

The calculation of the PK parameters of EE, LN, PSL and its metabolites ([redacted] [redacted] and [redacted] [redacted]) will be performed by the Pharmacokinetics, Pharmacodynamics, Modeling and Simulation Department, ICON PLC. All PK TFLs will be produced by ICON PLC SAS programming (Early Phase) or ICON Biostatistics. All PK tables and figures will be produced separately for each study part. All PK listings will be presented by study part.

Pharmacokinetic parameters of EE, LN, PSL and its two metabolites ([redacted] will be computed using the actual sampling time points.

The individual time-plasma concentrations of EE, LN, PSL, PSL metabolites, and PK parameters of EE, LN, PSL and PSL metabolites will be summarized by treatment (for EE and LN: OC alone and PSL+OC; for PSL and its two metabolites: PSL+OC and PSL alone) using descriptive statistics (number of observations, geometric mean, lower and upper 95% confidence intervals [CI], geometric coefficient of variation [CV], arithmetic mean, standard deviation [SD] and CV, median, and minimum and maximum value) and graphical displays. During the PSL + OC treatment period, two sets of PSL PK parameters will be analyzed: one set when PSL is

administered alone and the other set when PSL is administered with OC. Two sets of EE and LN PK parameters will be analyzed: one set during the PSL+OC treatment period and another during the OC alone treatment period.

All PK sampling time deviations will be calculated relative to the last dose of study medication. For sequence A, it will be on Day 19 for the PSL+OC period and on Day 34 for the OC alone period. For sequence B, it will be on Day 1 for the OC alone period and on Day 36 for the PSL+OC period. Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly.

9.1 Analysis of the primary pharmacokinetic variables

The primary PK variables in plasma used for EE and LN are C_{max} and AUC. C_{max} and AUC will be determined from the observed concentration and time data. AUC will be computed using the linear up/log down trapezoidal rule.

The PK individual time plasma concentrations and the primary PK parameters of EE and LN will be summarized by treatment (PSL+OC/OC alone), using descriptive statistics (number of available observations [n], arithmetic mean, median, standard deviation, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean [assuming log-normally distributed data]). Values below the LLOQ will be reported with a clear sign (flag variable in the dataset) indicating that they were below the LLOQ.

Individual study participant concentration-time profiles of EE and LN will be displayed graphically on both linear and semi-logarithmic scales. Spaghetti plots will be presented for all study participants per treatment (OC alone and PSL+OC) and analyte with all study participants overlaid on the same plot (linear and semi-logarithmic scale). Ping-pong plots will also be produced for C_{max} and AUC for EE and LN (with and without PSL).

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

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

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

Geometric mean profiles of plasma concentrations for EE and LN over time will be presented, with both treatments (PSL+ OC and OC alone) overlaid on the same plot, in both linear and semi-logarithmic scale. For the linear scale plot only, the lower and upper 95% confidence interval (CI) for the geometric mean will be displayed.

All plasma concentration figures will include the LLOQ on the semi-logarithmic scale plots and will be based on scheduled times.

9.2 Analysis of secondary pharmacokinetic variables

The secondary PK variables in plasma used for PSL are $C_{max,ss}$ and AUC_{τ}. $C_{max,ss}$ will be determined from the observed concentration and time data. AUC_{τ} will be computed using the linear up/log down trapezoidal rule.

Pharmacokinetic parameters ($C_{max,ss}$, C_{trough}, $AUC_{\tau,}$ metabolic ratio based on AUC_{τ} ($MR_{AUC\tau}$)) of PSL and its two metabolites will be compared between days with OC [Part 1: Day 13 for Sequence A and Day 30 for Sequence B; Part 2: Day 9 for Treatment Sequence A and Day 26 for Treatment Sequence B] and without OC [Part 1: Day 12 for Treatment Sequence A and Day 29 for Treatment Sequence B; Part 2: Day 8 for Treatment Sequence A and Day 25 for Treatment Sequence B] using analysis of variance on the log-transformed parameters and estimation of geometric ratio of PK parameters between days with their 90% CI will be provided. Ping-pong plots will also be produced for each study part for $C_{max,ss,}$ $AUC\tau$, $MR_{AUC\tau,}$ $MR_{Cmax,ss}$, CL_{ss}, $t_{1/2}$, for PSL (with and without OC).

The relationship between individual AUC ratio and individual C_{max} (with and without PSL) of EE and LN, and the exposure to PSL ($AUC\tau$) will be assessed by scatterplots and linear regression analyses (log-transformed and also untransformed data) presented for each study part.

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

9.3 Analysis of other pharmacokinetic variables

The other steady-state PK parameters for PSL are CL_{SS}/F, C_{min}, t_{max} and $t_{1/2}$.

The other steady-state PK parameters for the two PSL metabolites [redacted] include $C_{max,ss,}$ $AUC_{\tau,}$ $t_{max,}$ $t_{1/2,ss,}$ $C_{trough\ ,}$ $MR_{AUC\tau,}$ $MR_{Cmax,ss}$. $C_{max,ss}$ will be determined from the observed concentration and time data. AUC_{τ} will be computed using the linear up/log down trapezoidal rule.

The other PK parameters for EE and LN (single-dose oral contraceptive containing EE and LN) include $t_{max,}$ $AUC_{0\text{-}t,}$ $t_{1/2}$ and CL/F.

The other PK parameters will be summarized by study part and treatment using descriptive statistics (number of available observations [n], arithmetic mean, median, standard deviation, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean [assuming lognormally distributed data]). t_{max} will only display the number of available observations [n], median, minimum, and maximum.

Ping-pong plots will also be produced for $C_{max,ss,}$ and $AUC\tau$ separately for each study part for the two PSL metabolites ([redacted]).

10 SAFETY ANALYSES

All safety summaries and listings will be performed using the SS. All safety variables will be listed and summarized by study part, treatment sequence (Sequence A/Sequence B), treatment (PSL+OC / OC alone / PSL alone) and time point, when applicable.

10.1 Extent of exposure

All study medication (OC and PSL) administration details will be listed by study part, treatment sequence, and study participant. The listing will include the date and time of administration of the morning and evening dose and total daily dose of medication.

Exposure data will be listed only.

10.2 Adverse events

All AEs will be coded using the MedDRA® and characterized as pre-treatment and treatment-emergent according to the intake of the study medications (PSL, OC).

Adverse events with a start date prior to the first dose of study medication will be defined as pre-treatment AEs. For sequence A, the first dose of PSL is given on Day 1. For sequence B, the first dose of OC is given on Day 1.

A treatment-emergent AE (TEAE) is defined as any AE with a start date/time on or after the first dose of study medication (OC or PSL) or any unresolved event already present before administration of study medication that worsens in intensity following exposure to the treatment. Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of study medication. Missing or partially missing dates for AEs will be handled as described in Section 4.2.4.

Adverse events will be attributed to the treatment (OC, PSL or OC+PSL) after which they start. Thus, in **part 1**, for study participants randomized in Sequence A, all AEs starting after the first intake of PSL through Day 13 (prior to OC intake) will be attributed to PSL, all AEs starting after OC intake on Day 13 through Day 34 (prior to OC intake) will be attributed to PSL+OC, and all AEs starting after OC intake on Day 34 though Day 41 will be attributed to OC. In **part 1**, for study participants randomized in Sequence B, all AEs starting after the OC intake on Day 1 through Day 18 (prior to PSL intake) will be attributed to OC, all AEs starting after PSL intake on Day 18 though Day 30 (prior to OC intake) will be attributed to PSL, and all AEs starting after OC intake on Day 30 through Day 43 will be attributed to OC+PSL. In **part 2**, for study participants randomized in Sequence A, all AEs starting after the first intake of PSL through Day 9 (prior to OC intake) will be attributed to PSL, all AEs starting after OC intake on Day 9 through Day 26 (prior to OC intake) will be attributed to PSL+OC, and all AEs starting after OC intake on Day 26 though Day 33 will be attributed to OC. In **part 2**, for study participants randomized in Sequence B, all AEs starting after the OC intake on Day 1 through Day 18 (prior to PSL intake) will be attributed to OC, all AEs starting after PSL intake on Day 18 though Day 26 (prior to OC intake) will be attributed to PSL, and all AEs starting after OC intake on Day 26 through Day 35 will be attributed to OC+PSL. AEs starting more than 168 hours post last dose of study medication will be attributed to the SFU Period. A schematic summary is shown below.

Study Part	Sequence	PSL alone	PSL + OC	OC alone	SFU
1	A	Day 1 – 13 (prior to OC intake)	Day 13 (after OC intake) – 34 (prior to OC alone intake)	Day 34 (after OC intake) - 41	42+
	B	Day 18 (after PSL intake) – Day 30 (prior to OC intake)	Day 30 (after OC intake) - 43	Day 1 – 18 (prior to PSL intake)	44+
2	A	Day 1 – 9 (prior to OC intake)	Day 9 (after OC intake) – 26 (prior to OC intake)	Day 26 (after OC intake) - 33	34+
	B	Day 18 (after PSL intake) – 26 (prior to OC intake)	Day 26 (after OC intake) – 35	Day 1 – 18 (prior to PSL intake)	36+

All AEs will be recorded in the CRF from the time of informed consent until study completion or termination. All AEs will be coded (see Section 3.8) and categorized by intensity (mild/moderate/severe) and relationship (related/not related) to study medication (PSL, PSL+OC, and OC) as judged by the Investigator.

All AE data will be listed by study part, treatment sequence, study participant number, start date, 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 number and percentage of study participants who experience TEAEs will be summarized by MedDRA SOC, PT, treatment sequence and treatment period.

Summaries of TEAEs will include the following:

- Overview of incidence of TEAEs (overview including number and percentage of study participants with any TEAEs, any serious AEs, TEAE of Special Interest, TEAEs leading to discontinuation, drug-related TEAEs, severe TEAEs and TEAEs leading to death; event counts will also be included)
- Incidence of TEAEs by maximum relationship
- Incidence of TEAEs by maximum intensity
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants

Summary tables will contain counts of study participants, percentages of study participants in parentheses and the number of events where applicable. A study participant who has multiple events in the same SOC and PT will be counted only once in the study participant counts but all events will be included.

In summaries including relationship, the following relationships will be summarized: 'Not related', 'Related'. Study participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Study participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Incidence of Non-Serious TEAEs above reporting threshold of 5% of study participants will be reported by system organ class and preferred term.

Adverse event summaries will be ordered alphabetically by SOC and decreasing frequency of PT within SOC in the PSL+OC column for tables including event counts. For tables including only number and percentage of study participants, summaries will be ordered alphabetically by SOC and decreasing incidence of PT within SOC in the PSL+OC column.

Listings of AEs and TEAES will include the following:

- All AEs
- Incidence of all TEAEs
- All Serious AEs
- Discontinuation due to AEs.

All listings (except incidence of all TEAEs) will be presented by study part, treatment sequence (Sequence A/Sequence B) study participant and treatment period (PSL+OC/OC alone) and will include the SOC, PT, reported term, onset date/time and outcome date/time of the event (including relative days), the event duration (derived), time to onset (derived), pattern of event, intensity, relationship, action taken, outcome and AEs that led to discontinuation. TEAEs and SAEs will be flagged.

The listing of incidence of all TEAEs will be presented by study part and treatment sequence and will include intensity, relationship, severity, number of subject reporting a least one TEAE within SOC/PT, number of individual occurrences of TEAEs and site-participant number.

Additional summary tables of fatal, serious and discontinuation due to TEAEs by relationship will be produced if more than one of these events occurs.

10.3 Clinical laboratory evaluations

Laboratory data (clinical chemistry, hematology and urinalysis) and changes from Baseline (if applicable) will be summarized by descriptive statistics at each time point separately for each study part by treatment sequence for both absolute values and changes from Baseline. Shift tables from Baseline to each post-Baseline time point will be presented separately for each study part by treatment sequence. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. Only values outside the reference range for numeric variables will be listed. The reference ranges will also be reported in the listings.

A separate listing will present the study participant who meets one or more of the following criteria at any time point:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase ≥3x upper limit of normal (ULN)
- Total bilirubin increase ≥2xULN
- Alkaline phosphatase ≥2xULN

The listing will display only time points for which at least one of the above criteria was fulfilled for a given study participant, and will display all results obtained at time point for the specified variables.

A listing of study participants who meet the criteria for potential drug-induced liver injury (PDILI) will be presented together with any additional relevant data collected, if applicable.

Laboratory variables will be grouped according to the laboratory function panel (Table 10-1) and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory. For selected variables that are identified in Table 10-1 the change in category from Baseline will be presented in a shift table at all post-Baseline time points.

Any additional laboratory variables not included in the outputs described previously will be listed separately. These will include:

- Serology
- Alcohol breath test
- Serum pregnancy test (for women of childbearing potential)
- Urine drug screen

Table 10-1: Safety Laboratory measurements

Laboratory Assessments	Parameters			
Hematology	Platelet Count[c]	RBC Indices: MCV MCH Reticulocytes	WBC Count with Differential: Neutrophils[c] Lymphocytes[c] Monocytes Eosinophils Basophils	
	RBC Count[c]			
	Hemoglobin[c]			
	Hematocrit[c]			
	Coagulation panel			
	INR / Prothrombin			
Clinical Chemistry[a]	Blood Urea Nitrogen (BUN)[c]	Potassium	Aspartate Aminotransferase (AST[c])/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin

	Creatinine[c]	Sodium	Alanine Aminotransferase (ALT[c])/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase[c]	
Routine Urinalysis[b]	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick. If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.			
Other Screening Tests	• Follicle-stimulating hormone (at Screening only) to confirm postmenopausal status in female study participants • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Pregnancy test: Serum human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential) • Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab) The results of each test must be entered into the CRF.			

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

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

[c] Shift tables will be produced.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

The following vital signs measurements will be obtained with the study participants resting in the supine position for 5 minutes at all time points:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Respiratory rate
- Oral or aural body temperature

A by- study participant listing of all vital sign measurements and change from Baseline will be presented at each time point separately for each study part by treatment sequence.

Descriptive statistics will be reported for all vital sign measurements. Vital sign variables and changes from Baseline will be summarized by descriptive statistics at each time point separately for each study part by treatment sequence.

In case the treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) criteria are fulfilled, the results will be flagged.

Table 10-2: TEMA/PCS criteria for vital signs

Variable	Unit	Low[a]	High[a]
Systolic blood pressure	mmHg	Value <90 and ≥20 decrease from Baseline	Value >140 and ≥20 increase from Baseline
Diastolic blood pressure	mmHg	Value <50 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline
Pulse rate	bpm	Value <45 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline

bpm=beats per minute

[a] Both conditions must be satisfied for a measurement to be considered potentially clinically significant.

10.4.2 Electrocardiograms

12-lead ECG will be recorded 3 times at each time point. The individual means at each time point will be calculated as raw parameters for descriptive analysis. The individual mean and change from baseline will be summarized separately for each study part using descriptive statistics at each time point by treatment sequence.

All standard 12-lead ECG recordings will be taken in triplicate with the participant resting in the supine position for at least ≥5 minutes. The following ECG parameters will be reported:

- PR interval
- QT interval
- QRS interval
- QTc interval (QT corrected for heart rate using Fridericia's formula [QTcF])
- Heart rate

If available in the database, the QT corrected for heart rate using Bazett's formula (QTcB) will also be included in the listings and tabulations.

The individual measurements and the mean of the triplicate measurements will be reported in the by- study participant listings. The listing will also include the change from Baseline, based on the mean of the triplicate measurements at each time point, and will be presented by treatment sequence and by time point.

Measured values and changes from Baseline will be summarized at each time point and by ECG variable (based on the mean of the triplicate values at each time point). The mean change for

ECG parameter will also be displayed graphically separately for each study part by treatment sequence.

The following cut-points in QTcF, based on the mean of the triplicate data, will be summarized categorically (number and percentage of participants) at each time point.

For observed data:

- <450 msec
- ≥450 to <480 msec
- ≥480 to <500 msec
- ≥500 msec

Absolute change from Baseline in QTcF:

- <30 msec
- ≥30 to <60 msec
- ≥60 msec

All ECG findings for the individual triplicate measurements will be listed separately.

Any incomplete triplicate measurements at a given time point will be handled as described in Section 4.2.3.

Figures of mean change from Baseline in ECG parameters over time by treatment sequence will be displayed separately for each study part.

10.4.3 Other safety variables

10.4.3.1 Physical examination

Study participants with abnormalities in the physical examination will be listed by study part including details of the abnormality.

10.4.3.2 Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al, 2011) data will be listed by study part only. Module of the questionnaire, time point, question and the associated response will be listed for all the visit days where this questionnaire is collected. The listing will be based on the SS.

11 OTHER ANALYSES

A listing of comments will be presented.

12 REFERENCES

Phillips, A. and Haudiquet, V. (2003), ICH E9 guideline 'Statistical principles for clinical trials': a case study. Statist. Med., 22: 1-11. doi:10.1002/sim.1328

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266-77.

UCB Global Exploratory Development Guideline on performing NCA analysis. Version 1.0 08/NOV/2017

13 APPENDICES

Treatment	Sequence	Treatment	Overall
Study participant disposition	X		
Protocol deviations	X		
Demographics	X		
Medical history	X		
Lifestyle	X		
Prior medications	X		
Concomitant medications		X	X
Adverse Events		X	X
Laboratory tests	X		
Other safety continuous measurements (vital signs, ECG)	X		
Safety categorical results (laboratory shift tables, PDILI)	X		
PK plasma for PSL and its metabolites		X	
PK for EE and LN		X	

Approval Signatures

Name: up0035-sap

Version: 1.0

Document Number: CLIN-000146011

Title: up0035 - Statistical Analysis Plan

Approved Date: 29 May 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 29-May-2020 06:16:47 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 29-May-2020 12:12:14 GMT+0000