STATISTICAL ANALYSIS PLAN

Study: UP0050

Product: Padsevonil

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

SAP/Amendment Number	Date
SAP Final 1.0	22 January 2020

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LIST OF ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALQ	Above the Limit of Quantification
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ASPS	All Subject Participants Set
AUC	Area Under the Curve
AUC_{τ}	Area Under the Curve over a dosing interval
bid	twice daily dosing
BLQ	Below the Limit of Quantification
BUN	Blood Urea Nitrogen
CI	Confidence Interval
$C_{max,ss}$	maximum observed plasma concentration at steady-state
CRU	Clinical Research Unit
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ΔΔQTcF	placebo-corrected change from baseline
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of Study
HLGT	High Level Group Term
HLT	High Level Term
HR	Heart Rate
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IPD	Important Protocol Deviations
IUT	Intersection Union Test
LLOQ	Lower Limit Of Quantification
MedDRA	Medical Dictionary for Regulatory Activities

NCA	Noncompartmental Analysis
PD	Pharmacodynamic
PD-PPS	Pharmacodynamic Per-Protocol Set
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PR	Pulse Rate
PSL	Padsevonil
PT	Preferred Term
QTc	QT interval corrected
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate using the Fridericia method
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SFU	Safety Follow-Up
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures, Listings
t_{max}	time to maximum concentration
TQT	Thorough QT
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 UP0050. 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:

- Protocol amendment 1, dated 10 October 2019.
- Electronic case report form (eCRF), dated 24 October 2019.

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.

The content of this SAP is compatible with the International Council for Harmonization/Food and Drug Administration 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

The objectives and corresponding endpoints for this study are presented in Table 2-1.

Table 2-1: Objectives and endpoints

Objectives	Endpoints
Primary	
The primary PD objective is: • To evaluate the effects on cardiac repolarization (QTc interval) of high-dose PSL in comparison to placebo in healthy study participants	The primary PD endpoint is: • Placebo-corrected change from Baseline in QTc, based on Fridericia's correction (QTcF) method (ΔΔQTcF) evaluated during the Target Dose Day of the PSL and placebo Treatment Periods, using time point analysis
Secondary	
The secondary PD objective is: • To evaluate other aspects of the effects on cardiac function of high-dose PSL	The secondary PD endpoints are: • Placebo-corrected change from Baseline in QTcF after a single dose of moxifloxacin

in comparison with placebo and moxifloxacin	• Placebo-corrected changes from Baseline for HR, PR interval, and QRS interval • Frequency of treatment-emergent changes for T-wave morphology and U-wave presence • Change from Baseline in QTcF (ΔQTcF) evaluated at drug-specific t_{max} (Δt_{max}) for PSL, [redacted], [redacted], and possibly moxifloxacin
The secondary PK objective is: • To evaluate the plasma PK of PSL at steady state in healthy study participants	The secondary PK endpoints are: • $C_{max,ss}$, t_{max}, and AUC_{τ}, obtained from the plasma concentration-time profiles for PSL at steady state (on the Target Dose Day)
The secondary safety objective is: • To evaluate the safety and tolerability of PSL at the dosed level in healthy study participants	The secondary safety endpoints are: • Adverse events, SAEs, treatment-related AEs, and AEs leading to discontinuation of the study

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

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

Analysis of all endpoints except pharmacodynamics (PD) will be detailed in the current SAP. The analysis of PD endpoints will be conducted by ERT, and the planned analysis will be detailed in a separate SAP prepared by ERT.

2.2 Study design and conduct

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

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

The study schema is presented in Figure 2.1 and the schedule of activities is presented in Table 2-2.

Screening and Baseline Periods

The design uses a 3-Treatment Period crossover structure. Study participants who provide written informed consent will be screened within 28 days before the first Treatment Period. For further details regarding the assessments performed during the Screening and Baseline Periods, refer to the Schedule of activities (Table 2-2).

Treatment Periods 1, 2, and 3

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

Subsequently, dosing with the allocated study medication will be initiated: for study participants in the PSL Treatment Period, the bid doses of PSL will be titrated up to reach steady state in time for the target dose on the 'Target Dose Day,' as shown in Figure 2-1.

The randomized dosing regimen will be as follows :

In the PSL Treatment Period:

- On Day 1, 100mg PSL will be administered bid, in the morning and the evening.
- On Days 2 and 3, 200mg PSL will be administered bid, in the morning and the evening.
- On Days 4 and 5, 300mg PSL will be administered bid, in the morning and the evening.
- On Days 6 and 7, 400mg PSL will be administered bid, in the morning and evening.

- On Day 8, the Target Dose Day, study participants will be fasted prior to the morning dose. Subsequently, 400mg PSL will be administered in the morning, and placebo will be administered in the evening.
- On Day 9, 300mg PSL will be administered bid, in the morning and the evening.
- On Day 10, 200mg PSL will be administered bid, in the morning and the evening.
- On Day 11, 100mg PSL will be administered bid, in the morning and the evening.

In the Placebo Treatment Period:

- On Days 1 through 7, placebo to match the PSL treatment period doses will be administered bid, in the morning and the evening.
- On Day 8, the Target Dose Day, study participants will be fasted prior to the morning dose. Subsequently, placebo to match 400mg PSL will be administered in the morning, and in the evening.
- On Days 9 through 11, placebo to match the PSL treatment period doses will be administered bid, in the morning and the evening.

In the Moxifloxacin Treatment Period:

- On Days 1 through 7, placebo to match the PSL treatment period doses will be administered bid, in the morning and the evening.
- On Day 8, the Target Dose Day, study participants will be fasted prior to the morning dose. Subsequently, 400mg moxifloxacin will be administered in the morning, and placebo will be administered in the evening.
- On Days 9 through 11, placebo to match the PSL treatment period doses will be administered bid, in the morning and the evening.

On the morning of Day 1 of each treatment period, Holter ECG monitoring will be conducted at 0.75, 0.5, and 0.25 hours prior to the time of first dosing with study medication and until dosing, and a venous blood sample for PK analysis will also be drawn 0.5 hours prior to dosing. On the Target Dose Day of each Treatment Period (T1D8, T2D8, and T3D8), Holter ECG monitoring will be conducted from 1 hour prior to the morning dose of study medication and will continue for 24 hours after wards. For a full description of blood sampling time points, refer to the Schedule of activities (Table 2-2).

On the evening of the target dose day for each treatment period, all study participants will receive placebo in order to protect the 18 and 24-hour PK/QT evaluations during the PSL treatment period.

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

On days 12, 13, and 14 of each treatment period, study participants will remain at the clinic for inpatient follow-up assessments.

The safety and tolerability of repeated doses of PSL will be monitored throughout the study by evaluation of AEs, psychiatric and mental status, C-SSRS, vital signs, 12-lead ECG parameters,

physical and neurological examination findings, and clinical laboratory test results. The details of assessment of parameters refer schedule of activities (Table 2-2).

Washout Periods

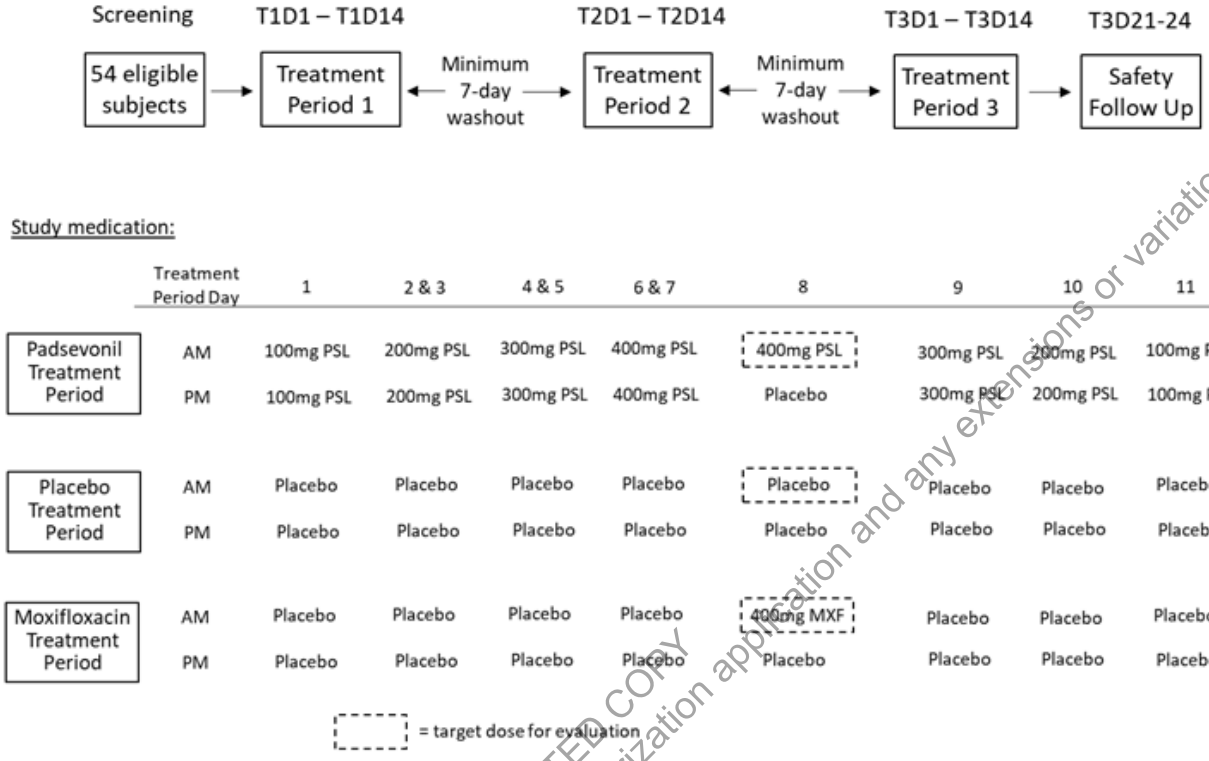
Following completion of each Treatment Period, study participants will be discharged from the clinic, returning on the day prior to the First Dosing Day of the next Treatment Period for readmission. The interval between Treatment Periods (Washout Period) will be sufficient to ensure a minimum of 7 days'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

Safety Follow-up Period

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

The study schema is presented in Figure 2-1 and the schedule of activities is presented in Table 2-2.

Figure 2-1: UP0050 Study Design



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

Table 2-2: Schedule of activities

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

Table 2-2: Schedule of activities

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

Table 2-2: Schedule of activities

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.3 Determination of sample size

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

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

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

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

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

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by ICON PLC and supervised by the Early Development Statistics Department of 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).

The PK noncompartmental analysis (NCA) will be performed using Phoenix WinNonlin®v6.3 or higher (Certara L.P., Princeton, NJ, USA) for PK parameter estimation using 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.

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.
- Unless otherwise stated, the denominator for the percentages will be based on the number of participants in the respective analysis set.

For continuous variables, summary statistics will include number of study participants (n), mean, median, 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 PK concentration data and PK parameters of PSL and its metabolites [redacted]).

When reporting descriptive statistics, the following rules will apply in general except for PK concentration data (plasma and urine PK) of PSL and its metabolites:

- n will be an integer.
- Mean, (arithmetic and geometric), SD 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 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.

Details on the presentation of PK concentration data (plasma and urine PK) of PSL and its metabolites are given in section 4.2.1.

3.2 General study level definitions

3.2.1 Relative day

The study day of an event will be derived relative to the date of first dose in treatment period 1.

Study days for an event or measurement occurring *before* the first date of drug intake are calculated as follows:

Study Day = Event Date - Date of first drug intake in first treatment period

The study day for an event or measurement occurring *on* the date of first drug intake is 1. The study day for an event or measurement occurring *after* the date of first drug intake will be calculated as follows:

Study Day = (Event Date - Date of first drug intake in first treatment period) + 1

There is no study Day 0. Study day will not be calculated for partial dates. In such cases, study day should be presented as "--"in the relevant participant data listing.

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

$$\text{Study Day} = + (\text{Event Date} - \text{Date of Last Dose in the last treatment period})$$

Period day of an event will be derived for each treatment period with the date of first drug intake in that corresponding period as reference.

The period day for an event or measurement occurring *on* the date of first drug intake is 1. The period day for an event or measurement occurring *after* the date of first drug intake will be calculated as follows:

Period Day = (Event Date - Date of first drug intake in that treatment period) + 1

There is no Period Day 0.

3.2.2 Study periods

The following study periods can be identified:

Screening and 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 the clinical research unit (CRU) 1 day prior to the each treatment period (on Day -1). Study participants will check-in at the CRU on Day -1.

Treatment Periods 1, 2, and 3: The study is designed as a crossover dosing across 3 treatment periods. Each treatment period consists of 14 days. The first dosing day will be Day 1, there is no Day 0. The first 2 treatment periods are followed by a wash-out period.

Washout Periods

After completion of a treatment period, study participants will be discharged from the clinic, returning on the day prior to the first dosing day of the next treatment period for readmission. The interval between treatment periods (washout period) will be sufficient to ensure a minimum of 7 days' washout from the study medication administered during the previous treatment period.

Safety Follow-up Period

After completion of the final treatment period, study participants will be discharged and return for a safety follow up (SFU) visit within 7 to 10 days after their discharge from the clinic.

3.3 Definition of Baseline values

Unless otherwise specified, baseline for each treatment period will be the last available pre-dose value prior to the first study drug intake in each treatment period, whether it is from scheduled or unscheduled measurements, ie there will be separate baseline values for each treatment period.

Treatment Periods	Baseline value
1	Prior to first dose in Period 1
2	Prior to first dose in Period 2
3	Prior to first dose in Period 3

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

$$Post\ Baseline\ Visit\ Value\ -\ Baseline\ Visit\ Value$$

Measurement-specific baseline time points are presented in the table below.

Table 3–1: Definition of Baseline

Variable	Baseline definition
Hematology, serum, chemistry, urinalysis	The baseline value is defined as the value from Day -1 of each treatment period. In case the Day -1 value of **first** treatment period is missing, the value obtained at the screening visit will be considered as baseline. If the day -1 value is missing for **treatment period 2 and/or 3**, the Day -1 value of the first treatment period will be considered.
Vital signs	The baseline value is defined as the last available pre-dose value on Day 1 of each treatment period. If the pre-dose day 1 value is missing for a treatment period, the value on Day -1 of that respective treatment period will be used.
ECG	12-lead ECG will be measured in triplicate. Baseline is the mean of the last three measurements prior to dosing for each treatment period. If less than three replicates are available, the mean of the available replicates (prior to dosing) will be considered as baseline.
C-SSRS	The baseline value is defined as the value from Day -1 of each treatment period. In case the Day -1 value of first treatment period is missing, the value obtained at the screening visit will be considered as baseline. If the day -1 value is missing for treatment period 2 and/or 3, the Day -1 value of the first treatment period will be considered.

ECG=electrocardiogram; C-SSRS= Columbia-Suicide Severity Rating Scale

3.4 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary outcome or key secondary outcome for an individual study participant. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the relevant protocol deviation specification document, which is part of the study data cleaning plan.

Important protocol deviations will include the following categories:

- Inclusion/exclusion criteria deviations
- Administration of prohibited concomitant medications
- Deviations relating to withdrawal criteria
- Visit schedule deviations
- Study drug administration deviations (including incorrect treatment received, handling and storage deviations and incorrect dosage received) and any vomiting episode(s) (that could impact PK concentrations)
- Procedural noncompliance
- Missing data

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

After all data have been verified/coded/entered into a database, a data evaluation meeting (DEM) will be performed.

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, define the analysis sets and check the quality of the data. The reviews will also help decide how to manage problems in the subjects' data (eg, 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 Set (ASPS) consists of all study participants who have signed the informed consent form. This set was previously referred to as Enrolled Set in the Study Protocol.

3.5.2 Safety Set

Safety Set (SS) defined as all study participants who receive at least 1 dose of study medication.

3.5.3 Pharmacokinetic Set

Pharmacokinetic Set (PKS): All study participants who receive at least 1 dose of study medication and who have no important protocol deviations affecting the PK and for whom at least 1 measurable PK concentration is available. This set has been referred to as PK-PPS (Pharmacokinetic Per Protocol Set) in the protocol.

3.5.4 Pharmacodynamic Per-Protocol Set

Pharmacodynamic Per-Protocol Set (PD-PPS) defined as all study participants who receive at least 1 dose of study medication and who have no important protocol deviations affecting the PD endpoint (ECG) and for whom at least 1 measurable value is available.

3.6 Treatment assignment and treatment groups

It is expected that participants will receive treatments as per the randomized treatment sequence and hence the analyses will be based on the randomized treatment. If a participant was randomized but not dosed in any treatment period, the participants results will be reported under the randomized treatment group.

Data collected only prior to dosing of first medication will be summarized per treatment sequence:

- Sequence ABC, ACB, BAC, BCA, CAB, CBA.

Code	Treatment
A	Padsevonil 400 mg
B	Placebo
C	Moxifloxacin 400 mg

Data collected during each of the 3 treatment periods will be summarized per treatment.

3.7 Center Pooling Strategy

Since this is a single center study this is not applicable.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the latest available version 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). 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

The randomized set (RS) has been deleted from the analysis sets and will no longer be used. All outputs which were initially planned for the RS will now be based on the SS.

The Enrolled Set has been renamed to All Study Participants set.

The PKPPS set has been renamed to PKS.

AUC_{0-t} has been added to the pharmacokinetic analysis.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No adjustments for covariates will be made.

4.2 Handling of dropouts or missing data

In general, there will be no imputation of missing data.

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.

The geometric CV will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

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

The Pharmacokinetic analysis will be performed in accordance to the Guideline on performing NCA analysis dated 08 Nov 2017.

4.2.1.1 PK concentrations

When reporting individual data in listings the following rules will apply:

- Missing data should be reported as NV (no value).
- Concentrations below the limit of quantification should be reported as BLQ (below the limit of quantification).
- Concentrations should be listed to the same number of significant figures supplied by the bioanalytical laboratory.

When reporting individual data in figures the following rules will apply:

- BLQ values prior to Cmax should be set to 0 for purposes of plotting the figure (to capture lag-time)
- Actual sampling times should be used

When summarising the data in tables the following rules will apply:

- To calculate descriptive statistics, BLQ values should be set to half the LLOQ value and missing values should be excluded
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this time point. Other descriptive statistics should be reported as missing ("-"). The minimum should be reported as "BLQ"
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ value replaced by half the LLOQ value"
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-")
- If no participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.

When summarising the data in figures the following rules will apply:

- The data plotted in the figure should match the data presented in the summary table, with the exception of missing values prior to Cmax which should be set to 0 in the figure (to capture lag-time)
- Geometric mean should be plotted (as opposed to arithmetic mean) due to the log-normal distribution of concentrations.Variability should be plotted as detransformed SD computed on ln-transformed data
- Nominal sampling times should be used
- Both linear and semi-logarithmic scales should normally be presented

4.2.1.2 PK parameters

When reporting individual data in listings the following rules will apply:

- Individual PK parameters should be reported to 3 significant figures.
- If a parameter cannot be calculated it should be reported as NE (not estimable ie if input data is missing which prevents calculation) or NC (not calculable ie if the data were available but the calculation was considered unreliable)

When summarizing the data in tables the following rules will apply:

- Generally descriptive statistics should be calculated on individual PK parameters that have 9 decimal places (exceptions include tmax and tlag ie discontinuous variables)
- For most PK parameters (ie for continuous variables) the following descriptive statistics should be calculated: mean, SD, geometric mean, CV, minimum, median and maximum. For tmax and tlag (ie for discontinuous variables) only median, minimum and maximum should be reported
- Descriptive statistics should be reported to 4 significant figures for the mean, median and standard deviation (SD) and to 3 significant figures for all others
- If at least two thirds of the subjects have a PK parameter reported then descriptive statistics will be calculated, otherwise only minimum and maximum will be reported for this PK parameter and all other descriptive statistics will be reported as NE (ie not estimable)
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-")

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".

The Pharmacokinetic analysis will be performed in accordance to the Guideline on performing NCA analysis dated 08 Nov 2017.

4.2.2 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 3 available measurements at a given time point, the mean will be calculated based on the number of measurements for which data are provided.

4.2.3 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.

4.2.4 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 3-1 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 3-1: 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

Table 3-1: Calculation rules for duration of adverse events			
Data availability	**Onset date/time**	**Outcome date/time**	**Calculation rules**
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a participant in the ASPS, 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
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. Repeated measurements are defined as more than 1 measurement at same time point. For example, the same lab parameters were assessed twice using the same batch of blood samples since the first assessment had issues. The following general rules will apply to all repeated and unscheduled measurements:

- Unscheduled and repeated measurements will not be used in the descriptive statistics at time points after first dose of study medication. For repeated measurements obtained after first dose of study medication, only the scheduled latest value can be used in the calculation of the descriptive statistics. For repeated measurements obtained prior to the first dose of study medication the latest value (which may be scheduled or unscheduled, sorting data by sampling date/time and take the last record) 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 measurements performed for the Early Withdrawal (EW) visit will be assigned to the EOS visit and analyzed accordingly as an EOS visit.

4.4 Interim analyses and data monitoring

No formal interim analyses are planned.

4.5 Multicenter studies

Not applicable as this is a single center study.

4.6 Multiple comparisons/multiplicity

No adjustments for multiplicity will be made.

4.7 Use of an efficacy subset of participants

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

4.8 Active-control studies intended to show equivalence

Not applicable.

4.9 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Participant disposition

The number of participants who signed the informed consent form, participants randomized, participants who completed or prematurely discontinued the study, as well as the reason for discontinuation will be summarized for all participants.. In addition, the number of participants who completed each treatment period will be included.

A participant who completed a treatment period is defined as a participant who has completed all visits belonging to that respective treatment period. A participant who completed the study is defined as a participant who completed all visits up to and including the EOS/ETV visit (in the Follow-up Period).

The number and percentage of participants included in each of the analysis sets will be summarized per treatment for all participants based on the ASPS.

In addition, the following listings will be presented:

- Participant disposition (ASPS).
- Participant analysis sets (ASPS).
- Discontinuation due to AEs (SS)

The listing of participant disposition will include the date of informed consent, date and time of first and last dose of drug per treatment period and overall, date of premature termination and primary reason (if applicable) for termination and date of final contact. An overview on the reasons for screen failure will be included.

The listing of study discontinuation will include the reason for premature study discontinuation, and the number of days on study medication per treatment.

The number of days on study medication will be calculated as follows:

$$Number\ of\ Days\ on\ study\ medication = (Date\ of\ Last\ Dose\ Received - Date\ of\ First\ Dose\ Received) + 1$$

The number of days on study medication will be calculated for each of the 3 treatment periods.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types in the IPD document.

A listing of all IPDs identified at the Data Evaluation Meeting will be presented for all participants based on the SS and will include the deviation type and description.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant (study participant) listing of demographics sorted by treatment sequence will be presented based on the ASPS. This will include the year of birth, age (in years), sex, race, ethnicity, height (in cm), baseline weight (in kg) and body mass index (BMI, in kg/m2). The height will be the measurement obtained at screening. Weight will be the last non-missing value prior to the first study drug intake at each treatment period. BMI documented in the CRF will be presented.

All demographic characteristics (except for year of birth) will be summarized for all participants based on the ASPS and SS by treatment sequence. The summary of age will include descriptive statistics.

Characteristics on experience of medical conditions will be also summarized for the SS and presented per treatment sequence.

The summary of age will include descriptive statistics and 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

6.2 Other Baseline characteristics

Lifestyle information (alcohol, drug abuse) for the subjects with DILI will be listed.

6.3 Medical history and concomitant diseases

Medical history will be listed for the SS by MedDRA system organ class (SOC), high level group term (HLGT), high level term (HLT), and preferred term (PT) per treatment sequence. The reported term will be included in the listing. The summary will include the number and percentage of 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 and concomitant medications will be listed and summarized separately for all participants in the SS, by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. Prior medications will be summarized by treatment sequence and concomitant medication by treatment periods. The reported term will be included in the listing.

Separate tabulations will be presented for prior medications and concomitant medications. Prior medications which continued into the first treatment period will also be classified as concomitant and will be included in both summaries.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in overall column.

6.4.1 Prior medication definition

Prior medications include any medications that started prior to the date of first intake of study drug in the first treatment period. This includes medications that started prior to the first dose and continued after.

6.4.2 Concomitant medication definition

Concomitant medications include any medications taken from the time of first drug administration in the first treatment period to a later point in the study. This includes medications that started prior to the first dose and continued after.

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

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study participant compliance will be ensured by the administration of study medication by designated site personnel. Drug administration must be recorded on the Study Medication Administration form. As all study drug is administered on site no formal calculations of compliance will be presented.

8 EFFICACY ANALYSES

Not applicable

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacodynamics

Full details on the analysis of the pharmacodynamics endpoints will be provided in a dedicated cardiac SAP.

9.2 Pharmacokinetics

9.2.1 Analysis of secondary pharmacokinetic variables

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

The PK parameters will be listed and summarized for participants who received PSL treatment using descriptive statistics (number of available observations [n], median, SD, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean [assuming log normally distributed data]) for PSL and its metabolites.

9.2.2 Analysis of other pharmacokinetic variables

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

The planned other PK endpoints of the major metabolites of PSL [redacted] include the parameters AUC_{0-12}, C_{max}, t_{max}, and metabolic ratios for C_{max} and AUC0-12 (single dose) and AUC_t, AUC_{0-t}, $CL_{ss/F}$, Ctrough, Cmax,ss, t_{max} and metabolic ratios for $C_{max,ss}$ and AUC_τ (multiple dose).

If required, the planned other PK endpoints of moxifloxacin including the parameters AUC, AUC_{0-t}, $t_{½}$, C_{max}, and t_{max} (single dose) will be calculated. In this case, these results will be reported in an addendum to the CSR.

The individual plasma concentrations and PK parameters of PSL, [redacted], and available moxifloxacin will be summarized by day (single dose day 1 or multiple dose, day 8) using descriptive statistics (number of available observations [n], median, standard deviation, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean [assuming log-normally distributed data]). In addition all data will be listed.

Individual participant plasma concentration-time profiles of PSL and its metabolites will be displayed graphically in linear and semi-logarithmic scale.

Combined individual (spaghetti) plasma concentration-time profiles plots will be displayed for PSL and its metabolites with all participants overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of plasma concentrations for PSL and its metabolites over time will be presented, in both linear and semi-logarithmic scale for Day 1 and Day 8. 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.

The C_{trough} concentration for PSL and its metabolites over time (Day 2 to 12) will be presented graphically.

In addition, box plots for the PSL PK parameters C_{max}, t_{max} and AUC_τ at day 1 (100 mg) and day 8 (400 mg) will be provided. In these plots the PK parameter will be on the y-axis, whereas the timepoint (Day 1 and Day 8, respectively) will be on the x-axis.

10 SAFETY ANALYSES

All safety listings will be performed using the SS and summarized by each treatment (PSL, Moxifloxacin, Placebo) and overall.

10.1 Extent of exposure

All study medication administration details will be listed by study participant. The listing will include the fasting state, dose, number of tablets taken, 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 categorized by intensity (mild/moderate/severe) and relationship (related/not related) as judged by the Investigator.Adverse Events will be categorized as Pre-treatment AEs, TEAEs, or Post-Treatment Period TEAEs (PTP-TEAEs), according to the intake of study drug. A treatment-emergent AE (TEAE) is defined as any AE with a start date/time on or after the first dose of study medication or any unresolved event already present before administration of study medication that worsens in intensity following exposure to the treatment. The following definition will be applied:

Pre-treatment AE: Any AE that starts prior to the date of the first dose of study drug (in the first treatment period).

TEAE: Any AE that starts on or after the date of the first dose of study drug and on or before the last date of the last treatment period (T3D14) or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment.

PTP-TEAE: Any AE that starts after the date last inpatient FU day of the last treatment period i.e. occurring during the SFU Period.

Any event occurred during washout period will be considered treatment emergent and attributed to the most recent treatment received (ie. the treatment of the previous period).

Missing or partially missing dates for AEs will be handled as described in Section 4.2.4. 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, or AE started during SFU. Adverse events will be attributed to the treatment in which they started.

The number and percentage of participants who experience TEAEs will be summarized by MedDRA system organ class (SOC), preferred term (PT) and treatment.

Summaries of TEAEs will include the following:

- Incidence of TEAEs (overview including number and percentage of participants with any TEAEs, serious TEAEs, TEAE of special interest (TEAESI), discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs, all deaths (AEs leading to death regardless of treatment emergence) and TEAEs leading to death; event counts will also be included).

The TEAEs will be summarized and tabulated at both the study participants (number and percentage of participants) and event (number of events) level wherever applicable:

- TEAEs by treatment, SOC, PT, and maximum reported severity grade (mild, moderate, severe).
- TEAEs by treatment, SOC, PT, and maximum relationship to study drug.
- Non-serious TEAEs above reporting threshold of 5% by treatment, SOC, PT.

A participant who has multiple events in the same SOC and PT will be counted only once in the participant counts for that treatment but all events will be included.

In summaries including relationship, the following relationships will be summarized: “Not related” and “Related”. If a participant reports the same event with different relationship assessments, the participant is counted under related. As such, each subject will be counted

once within each System Organ class and Preferred Term. 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'. 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.

Adverse event summaries will be ordered alphabetically by SOC, within each SOC, PTs will be sorted by decreasing frequency of "All Participants" column for tables.

A listing for all AEs will be presented by participant and treatment sequence. The listings will include the following data pertaining to the AEs: SOC, HLT, PT, reported term, start and end dates with relative days to study medication administration (per period), duration, intensity, seriousness, relationship to study medication, action taken, and final outcome. In addition, separate listings will be provided for the incidence of all TEAEs, SAEs and AEs leading to discontinuation.

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

10.2.1 Adverse event of special interest (AESI)

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AESI. Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the participant.

Therefore a separate listing will present the study participants who meet 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 that time point for the specified variables.

10.3 Clinical laboratory evaluations

Laboratory data (clinical chemistry, hematology and urinalysis) and changes from baseline (if applicable) for numeric variables will be listed by participants, parameter, treatment sequence and time point. Only abnormal laboratory values will be listed. In case of any abnormal value, all values for the respective subject on this laboratory parameter will be listed.

Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.3. Values outside the reference range for numeric variables will be flagged in the listings and in addition, will be listed separately for each lab category (hematology, chemistry and urinalysis). The reference ranges will also be reported in the listings.

Clinical chemistry, hematology, and urinalysis parameters will be summarized by treatment and time point for both absolute values and changes from baseline.

Shift tables from baseline to each post-baseline time point will be presented by treatment period for selected hematology and chemistry parameters (see Table 10.1).

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.

Additionally the following laboratory variables will be listed by treatment sequence:

- Serology
- Urine Drug Screen
- Alcohol detection test
- Serum and urine pregnancy test (for women of childbearing potential)

In addition, potential drug induced liver injury (PDILI) data will be listed by treatment sequence. This will include laboratory results meeting the PDILI categories as mentioned below:

- ALT increase ≥3xULN or AST increase ≥3xULN
- ALP ≥2xULN
- Total Bilirubin increase ≥2xULN.

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

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

Table 10-1: Protocol-required safety laboratory assessments

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

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

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

- Systolic and diastolic blood pressure (standing position at screening only)
- Pulse rate
- Temperature
- Respiration rate

A by-participant listing of all vital sign measurements and change from baseline will be presented by treatment sequence and time point.

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 by treatment.

In case the TEMA/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; PCS=potentially clinically significant; TEMA=treatment-emergent markedly abnormal.
[a] Both conditions must be satisfied for a measurement to be considered potentially clinically significant.

10.4.2 Electrocardiograms

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

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:

- Heart rate
- PR interval
- RR Interval
- PQ/PR interval

- QRS interval
- QT Duration
- QTcB interval (QT interval corrected for HR according to Bazett's formula)
- QTcF

The individual measurements and the mean of the triplicate measurements will be reported in the by-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 time point. ECG findings will also be listed.

The following cut-points in QTcF, based on the mean of the triplicate data, will be summarized categorically (number and percentage of participants) by treatment 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

10.4.3 Other safety variable(s)

10.4.3.1 Physical examination

Participants with abnormalities in the physical examination will be listed including details of the abnormality.

10.4.3.2 Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale (C-SSRS) data will be listed 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.

11 OTHER ANALYSES

No other analysis planned.

12 REFERENCES

- Columbia University Medical Center. Columbia-Suicide Severity Rating Scale (2008). http://www.cssrs.columbia.edu/.
- Electronic case report form (eCRF) dated 24 October 2019.
- Food and Drug Administration. Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrythmic Drugs-Questions and Answers (R3), Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 06/2017.
- Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018 Jun;45(3):383-97.
- 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
- Protocol amendment 1 dated 10 October 2019.
- Zhang J and Machado SG. Statistical issues including design and sample size calculation in thorough QT/QTc studies. J Biopharm Stat. 2008;18(3):451-67

13 APPENDICES

Table 13-1: Breakdown of treatment group reported into the TFLs by study assessment data

	Analysis Set			Treatment Sequence	Treatment	
	Table	Figure	Listing		PSL/Moxifloxacin/ Placebo	All Participants
Study participant disposition	ASPS		ASPS		X	X
Protocol deviations			SS	X		X
Study participant Discontinuation	SS		SS	X		X
Participants analysis sets	ASPS		ASPS	X		X
Demographics & Baseline Characteristics	ASPS		SS	X		X
Medical history	SS		SS	X		X
Prior medications	SS		SS	X		X
Concomitant medications	SS		SS		X	X
Study Drug Administration			SS	X		X
PD Parameter	PD-PPS		PD-PPS		X	X
PK Conc. Individual	PKS	PK-S	PKS		X	X
PK Parameter	PKS	PKS	PKS		X	X
Adverse Events	SS		SS		X	X
Lab (Hematology, Chemistry, Urinalysis)	SS		SS		X	X
Lab (Virology, Serology, Alcohol)	SS		SS	X		X
PDILI			SS		X	X
Urine sampling (pregnancy, drug screen)			SS	X		X
Vital signs	SS		SS		X	X
12-lead ECG	SS	SS	SS		X	X
Physical Examination			SS	X		X
C-SSRS			SS	X		X

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