STATISTICAL ANALYSIS PLAN

Study: UP0053

Product: Padsevonil

AN OPEN-LABEL, PARALLEL-GROUP, PHARMACOKINETIC, SAFETY AND TOLERABILITY STUDY OF SINGLE AND MULTIPLE ORAL ADMINISTRATIONS OF PADSEVONIL IN ADULTS AND ELDERLY STUDY PARTICIPANTS

SAP/Amendment Number	Date
SAP Version 1.0	18 Sep 2019

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
ALT	alanine aminotransferase
ALQ	above the limit of quantification
AST	aspartate aminotransferase
AUCτ	area under the curve over a dosing interval
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CL/F	apparent total clearance
CL/F_{ss}	apparent total clearance at steady-state
C_{max}	maximum observed plasma concentration
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
EOS	End of Study
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration

f_e	Fraction of the dose excreted unchanged
fe_{met}	Fraction of the dose excreted as the metabolite
FU	Follow-up
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
MedDRA	Medical Dictionary for Regulatory Activities
MD	Multiple dose
MHD	Mono Hydroxy Derivate
MW	Molecular Weight
n	number of participants number of available observations
NCA	Noncompartmental analysis
PK-PPS	Pharmacokinetic-Per Protocol Set
PK	Pharmacokinetic(s)
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 dose
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures and listings
t_{max}	time to maximum concentration
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 UP0053. 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:

- Final protocol, including the protocol amendment 1 dated 29 May 2019 and the original protocol dated 07 May 2019.
- The protocol clarification memos dated 11 June 2019 and 11 September 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 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 (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is to evaluate the plasma pharmacokinetics (PK) of Padsevonil (PSL) in adult and elderly study participants.

2.1.2 Secondary objectives

The secondary objectives of this study are to:

- Evaluate the urine PK of Padsevonil in adult and elderly study participants.
- Evaluate the safety and tolerability of Padsevonil in adult and elderly study participants (AE specific endpoints).

2.1.3 Other objectives

The other objectives of this study are to:

- Evaluate the plasma PK of Padsevonil and two of its metabolites [redacted]) in adult and elderly study participants:
- Evaluate the urine PK of Padsevonil and two of its metabolites [redacted] in adult and elderly study participants:

- Evaluate the relationship between creatinine clearance and hepatic function tests and the PK of Padvesonil and two of this metabolites [redacted]) in adult and elderly study participants:
- Further evaluate the safety and tolerability of Padsevonil in adult and elderly study participants (Laboratory, vital signs, ECG and PE related endpoints).

2.2 Study variables

2.2.1 Pharmacokinetic variables

2.2.1.1 Primary pharmacokinetic variables

The primary PK variables will be Cmax, AUC_{0-t} and AUC for the single dose and $C_{max,ss}$ and AUC_{τ} for the multiple dose obtained from the plasma concentration-time profiles for PSL:

- C_{max}: maximum observed plasma concentration
- AUC_{0-t}: area under the curve from time 0 to the last quantifiable concentration
- AUC: Area under the curve from time 0 to infinity
- $C_{max,ss}$: maximum observed plasma concentration at steady-state
- AUC_{τ}: area under the curve over a dosing interval

2.2.1.2 Secondary pharmacokinetic variables

The secondary PK variables will be the amount of PSL and its metabolites excreted in urine and the metabolic ratio of amount excreted in urine.

- Ae: Cumulative amount of PSL or its metabolite excreted in urine
- MR_{Ae}: Metabolic Ae ratio

2.2.1.3 Other pharmacokinetic variables

The following other PK variables for PSL and the two metabolites of PSL will be assessed during the study (single dose and multiple dose):

<u>For the plasma PK of PSL:</u>

Bound and unbound plasma concentration of PSL in two samples

Single Dose:

- CL/F: apparent total clearance

Multiple Dose

- CL/Fss: apparent total clearance at steady-state

<u>For the plasma PK of the two metabolites of PSL:</u>

Single Dose:

- C_{max}: maximum observed plasma concentration
- AUC_{0-t}: area under the curve from time 0 to the last quantifiable concentration

- AUC: Area under the curve from time 0 to infinity

Multiple Dose

- $C_{max,ss}$: maximum observed plasma concentration at steady-state
- AUC_{τ}: area under the curve over a dosing interval

For the plasma PK of PSL and the two metabolites of PSL:

- C_{trough}: Measured concentration at the end of a dosing interval at steady state
- t_{max}: time of C_{max} or $C_{max,ss}$
- $t_{1/2}$: Terminal elimination half-life
- $t_{1/2,ss}$: Terminal elimination half-life at steady-state
- AUC_{0-12}: area under the curve from time 0 to 12h after a single PSL dose
- $MR_{AUC\tau}$: Metabolic ratio for AUC_{τ}
- $MR_{Cmax,ss}$: Metabolic ratio for $C_{max,ss}$

For the urine PK

- CL_R: Renal clearance of PSL
- fe : Fraction of the dose excreted unchanged
- fe_{met}: Fraction of the dose excreted as the metabolite

2.2.2 Safety variables

2.2.2.1 Secondary safety variables

The following secondary safety variables will be assessed during the study:

- Incidence of Treatment Emergent Adverse Events (TEAEs)
- Incidence of Serious Adverse Events (SAEs) and
- Incidence of TEAEs leading to discontinuation.

2.2.2.2 Other safety variables

The following other safety variables will be assessed during the study:

- Changes in safety laboratory data (hematology, clinical chemistry and urinalysis)
- Changes in vital signs (pulse rate (PR), systolic and diastolic blood pressure (BP), respiratory rate (RR) and body temperature)
- Changes in 12-lead electrocardiogram (ECG) assessment
- Physical examination findings

2.3 Study design and conduct

This is a Phase 1, open-label study to evaluate the effect of age on the PK, safety, and tolerability of oral PSL in 2 cohorts of at least 10 adult (18 to 64 years, inclusive) study participants (Cohort A) and 18 elderly (≥65 years) study participants (Cohort B).

The study utilizes a single dose (SD) and a multiple dose (MD) design. Period 1A is the SD Period and consists of a single dose of PSL followed by a Washout Period. Period 1B is the MD Period and consists of PSL up-titration, maintenance, and tapering during the Treatment Period, followed by a Washout Period. Both adult and elderly study participants will take part in the SD and MD Periods.

The total study duration for each study participant is up to 28 days for Screening plus 22 days from Day 1 through the EOS/EOT Visit (up to 50 days in total).

The study consists of Screening, a Baseline Visit, Treatment Period, and Follow-up Period (End-of-Study/End-of-Treatment [EOS/EOT] Visit).

Screening will be conducted at the study site(s) 3 to 28 days prior to check-in to the study site. Eligible study participants in the 2 age cohorts will be matched per gender for body weight if feasible, i.e., the elderly study participants will be recruited first, and per gender, matched for body weight with adult study participants. Individual cases will be discussed with the Sponsor as needed. In each age cohort, there will be a homogenous repartition between male and female study participants, with at least 3 participants in each gender. To allow for an investigation of potential age-dependent effects, the elderly study participant cohort will also preferably include the following categories: at least 3 males and 3 females from ≥65 to 74 years old, and at least 3 males and 3 females ≥75 years old.

Study participants will check into the study site on Day -1 for the Baseline Visit and will undergo assessments as specified in the Schedule of Activities (Table 2–1).

The Treatment Period consists of Period 1A (PSL SD administration) on Days 1 to 7 and Period 1B (PSL MD administration) on Days 8 to 21.

In Period 1A, study participants will receive a single oral dose of 200mg PSL on Day 1, at approximately 8:00am, 30 minutes after a light meal. No study drug will be administered on Days 2 to 7; assessments will be conducted during this time as specified in the Schedule of Activities (Table 2–1). Days 2 to 7 are designated as a 6-day washout.

In Period 1B, study participants will receive multiple oral doses of PSL as follows (note: twice daily [BID] dosing is achieved with a morning [approximately 8:00am] and evening [approximately 8:00pm] dose):

Day 8: 50mg PSL BID

Day 9: 100mg PSL BID

Days 10 to 12: 200mg PSL BID

Day 13: A morning dose of 200mg PSL and an evening dose of 100mg PSL

Days 14 and 15: 100mg PSL BID

Day 16: 50mg PSL BID

Days 17 to 21: no PSL administration; 5-day washout

Throughout the study, plasma and urine samples for PK analysis and safety evaluations will be obtained according to the Schedule of Activities (Table 2–1). Adverse events and concomitant medications will be recorded throughout the study. Liver function parameters and creatinine clearance will be assessed in each study participant. These parameters are influenced by age; therefore, the acceptance ranges for these tests are wider for the elderly study participants.

On Day 22, study participants will complete the EOS/EOT Visit procedures as specified in the Schedule of Activities (Table 2–1).

Dropouts may be replaced at the discretion of the Investigator and Sponsor

Table 2–1 Schedule of activities

Study Period/Visit	Scr	BL Visit	Treatment Period															Follow-up Period
			Period 1A (SD)						Period 1B (MD)									EOS/ EOT Visit
Study Day(s)	**-28 to -3**	**-1**	**1**	**2**	**3**	**4**	**5-7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17-21**	**22**
			Washout														Washout	
Procedures																		
Written Informed Consent	X																	
Demographics & baseline characteristics	X	X																
Inclusion/exclusion criteria verification	X	X																
General medical/procedures history	X	X																
Study Participant Identification Card assigned		X																
Suicidality risk evaluation (C-SRSS) [a]	X	X				X										X		X
Physical examination [b]	X	X	X			X		X								X		X
Psychiatric and Mental Status	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X
Vital signs [c]	X	X	X				X	X	X	X	X	X	X	X	X	X		X
Pregnancy test [d]	X	X																X
Hematology, serum chemistry, urinalysis [e]	X	X				X		X					X			X		X
Serology (HIV, Hep B & C)	X																	
12-lead ECG [f]	X	X	X					X	X	X	X	X	X	X	X	X		
Urine and cotinine drug screen, alcohol breath test	X	X						X										
Recording of AEs /medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period/Visit	Scr	BL Visit	Treatment Period															Follow-up Period
			Period 1A (SD)						Period 1B (MD)									EOS/ EOT Visit
Study Day(s)	-28 to -3	-1	1	2	3	4	5-7	8	9	10	11	12	13	14	15	16	17-21	22
			Washout														Washout	
Procedures																		
Admit to study center		X [g]					X[g]											
Discharge from study center							X[g]										X[g]	X
Administer PSL			X					X	X	X	X	X	X	X	X	X		
Study drug accountability			X						X	X	X	X	X	X	X	X		
Blood sampling for PSL PK levels [h]			X	X	X	X							X					
Additional blood sampling for PPB [i]													X					
Urine collection for PSL PK [j]			X	X	X	X							X					
Final disposition determination [k]																		X

AE=adverse event; BID=twice daily; BL=Baseline; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; Hep=hepatitis; HIV=human immunodeficiency virus; MD=multiple dose; PK=pharmacokinetic(s); PPB=plasma protein binding; PSL=padsevonil; Scr=screening; SD=single dose; t_{max}=time to maximum plasma concentration

[a] All study participants will complete the "Screening/Baseline" version of the C-SSRS during Screening (assessing the past 6 months) and Baseline (Day -1), followed by the "Since Last Visit" version at subsequent visits.

[b] 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 short physical examination (see Section 8.3.4 of the study protocol).

[c] Vital signs will be performed before each morning dose of PSL; if feasible; vital sign evaluations will follow the same schedule as ECGs. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the study participant in a quiet setting without distractions (eg, television, cell phones).

[d] Serum pregnancy test will be performed for females of childbearing potential at Screening. Urine pregnancy testing will be performed at all other time points indicated.

[e] For safety laboratory evaluations that occur on a dosing day, these will be performed before the morning dose/PK sample collection.

[f] A 12-lead ECG will be performed after a rest of at least 5 minutes. All ECG recordings will be performed in triplicate at 2 to 3 minute intervals at Screening, Baseline (Day -1), predose and 3 hours after the morning dose on each PSL dosing day and EOS/EOT Visit.

[g] Study participants will be confined to the study site starting at Baseline (Day -1) and may be discharged on the morning of Day 5 after the assessments are complete, per the discretion of the Investigator. Study participants discharged on Day 5 will be readmitted to the study site on the evening of Day 7. If the Investigator deems it acceptable, study participants may be discharged the morning of Day 17.

[h] PK plasma samples will be taken at the following time points: (a) Period 1A (single dose): predose on Day 1 and 0.25, 0.5, 0.75, 1, 1.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose (14 samples); (b) Period 1B (multiple doses): predose (morning dose), and 0.25, 0.5, 0.75, 1, 1.5, 3, 4, 6, 8, and 12h after the morning dose (11 samples).

[i] Two blood samples will be collected after multiple doses at steady state (Day 13 predose and 1.5h postdose[(~t_{max}]) for PPB.

[j] After the morning urine void and collection of a predose sample (no more than 60 minutes before dosing), PK urine collection will be performed at regular intervals on Days 1, 2, 3, and 4 at the following time points: 0 to <12h; 12 to <24h, 24 to <48h, and 48 to <72h after the single dose (4 samples). On Day 13, PK urine collection will be performed 0 to 12h after the 200mg PSL morning dose (1 sample).

[k] For study participants prematurely terminating or completing the study, final disposition is recorded at the EOS/EOT Visit. All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures, in accordance with the EOS/EOT Visit schedule, as soon as possible after the last dose of study medication.

2.4 Determination of sample size

No formal sample size computation has been performed for this study. This PK study will be a study of limited size conducted under SD and steady-state conditions to look for sizable differences between adult (18 to 64 years of age) and elderly (≥65 years of age) study participants. A total of 28 study participants (10 study participants of age 18 to 64 years and 18 study participants of age ≥65 years) is planned.

A sample size of 9 study participants in each age group will have 97% power to detect a fold change in means (expected ratio) of 2.0, assuming that the coefficient of variation is 40% using a 2 group t-test with a 0.05 1-sided significance level.

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. Individual plasma and urine concentration 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 participants in the respective analysis set.

Continuous variables will be summarized by visit and time point (where applicable) including number of study participants (n), mean, median, standard deviation (sd), minimum, 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 concentration and PK parameters for PSL and two metabolites of PSL [redacted]). In all outputs the confidence limits will be restricted to the possible values that the variable can take.

When reporting descriptive statistics, the following rules will apply in general except for PK concentration data (plasma and urine PK) of PSL and two metabolites of PSL [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 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 (plasma and urine PK of PSL and two metabolites of PSL, [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 (plasma and urine PK of PSL and two metabolites of PSL [redacted], and parent to metabolite ratio) 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 age group (Adults (18-64 years) and Elderly (>=65 years)).

3.2 General study level definitions

3.2.1 Relative day

The relative day of an event will be derived with the date of first dose of investigational medicinal product (IMP), here PSL as reference.

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

$$Relative\ Day = Event\ Date - Date\ of\ First\ Dose\ in\ the\ treatment\ period$$

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

$$Relative\ Day = (Event\ Date - Date\ of\ First\ Dose\ in\ the\ treatment\ period) + 1$$

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

$$Relative\ Day = +\ (Event\ Date - Date\ of\ Last\ Dose\ in\ the\ treatment\ period)$$

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

3.2.2 Study periods

For each participant completing the study, the expected maximum duration of participation will be approximately 50 days with a maximum of 10 days exposure to investigational product, and will consist of the following periods:

- Screening Period (Day -28 to Day -3)

  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 Treatment Period. Study participants will check-in at the CRU on Day -1.

- Treatment Period 1A (PSL SD administration) (Day 1 to Day 7)

  In Period 1A study participants will receive a single oral dose of 200mg PSL on Day 1, at approximately 8:00am, 30 minutes after a light meal has finished. No study drug will be administered on Days 2 to 7; assessments will be conducted during this time as specified in the Schedule of Activities (Table 2–1). Days 2 to 7 are designated as a 6-day washout.

- Treatment Period 1B (PSL MD administration) (Day 8 to Day 21)

  In the Period 1B study participants will receive multiple oral PSL doses on Days 8 to 16, followed by a 5-day washout (Days 17 to 21). Padsevonil will be administered BID, with one dose in the morning [approximately 8:00am] and one dose in the evening [approximately 8:00pm]. The specific PSL dosing schedule is as follows:

  Day 8: 50mg PSL BID

  Day 9: 100mg PSL BID

Days 10 to 12: 200mg PSL BID

Day 13: A morning dose of 200mg PSL and an evening dose of 100mg PSL

Days 14 and 15: 100mg PSL BID

Day 16: 50mg PSL BID

Days 17 to 21: no PSL administration; 5-day washout

- The Follow-Up Period consists of an End of Treatment (EOT) /End of Study (EOS) Visit performed on Day 22 after discharge or upon discontinuation of the study.

The end of the study is defined as the date of the last visit of the last participant in the study.

3.3 Definition of Baseline values

Baseline will be the last non-missing value prior to first PSL dosing in each period (Period 1A (SD) and Period 1B (MD)). Scheduled or unscheduled measurements can be used as the Baseline value.

If a measurement is repeated at Baseline or a given treatment period and is obtained prior to dosing, then the last available measurement will be used as the Baseline value.

12-lead ECG will be measured in triplicate. The mean of the last three predose measurements will be taken as the baseline; if less than three predose replicates are available, the mean of the available predose replicates will be taken as the baseline.

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 with an important protocol deviation will be excluded from the FAS. Study participants will be excluded from FAS only when there is documented evidence that they received no treatment. Study participants may be excluded from the PK Per Protocol Set (PK-PPS) 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 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 consist of all study participants who have signed the Informed Consent form (ICF).

3.5.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all study participants who have signed the ICF and received at least one dose of investigational medicinal product (IMP). Analysis of this set will be according to the treatment the study participants actually received. All safety analyses will be performed using the FAS.

3.5.3 Pharmacokinetic-Per Protocol Set

The Pharmacokinetic-Per Protocol Set (PK-PPS) is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PK parameters and had a sufficient number of samples available to determine at least one PK parameter.

All PK analyses will be performed using the PK-PPS.

3.6 Treatment assignment

Tables will be presented by age group (Adults (18-64 years) or Elderly (>= 65 years)) and overall. Listings will be presented by age group and study period as described in Section 3.2.2. PK summaries will be presented for PSL and two metabolites of PSL during the treatment periods (SD and MD)

Table 3–2: Padsevonil administration

	Cohort A (adults; n=at least 10) and Cohort B (elderly; n=at least 18)																
	Treatment Period																Follow-up Period
	Period 1A (SD)					Period 1B (MD)											EOS/ EOT Visit
Day	**1**	**2**	**3**	**4**	**5 to 7**	**8**	**9**	**10**	**11**	**12**	**13 morning**	**13 evening**	**14**	**15**	**16**	**17 to 21**	**22**
		Washout														**Washout**	
PSL Dose (mg)	200					50 BID	100 BID	200 BID	200 BID	200 BID	200	100	100 BID	100 BID	50 BID		
	Plasma	Plasma	Plasma	Plasma							Plasma						
	Urine	Urine	Urine	Urine							Urine						

BID=twice daily; EOS=End-of-Study; EOT=End-of-Treatment; MD=multiple dose; PK=pharmacokinetic(s); PSL=padsevonil; SD=single dose
Note: BID dosing will be at approximately 8:00am and 8:00pm.
Note: To allow age-dependent effects, elderly study participants will include preferably the following categories: at least 3 males and 3 females from ≥65 to 74 years old and at least 3 males and 3 females ≥75 years old. The elderly study participants will be analyzed as one group. If an effect of age category is observed on PK or safety parameters, the effect of the age category will be explored.

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 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) (Version SEP/2017). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

- Changes in the analysis of PK variables (section 1.1 of the protocol):
  - The analysis of CL/F_{ss} (apparent total clearance at steady-state) will be conducted only for PSL and not for the two metabolites of PSL (as planned in protocol section 1.1).
  - The variable $MR_{Cmax,ss}$ (Metabolic ratio for $C_{max,ss}$) will be analysed for PSL and two metabolites of PSL instead of the variable MR_{Cmax} (Metabolic ratio for C_{max}).
- Change in the name of an analysis datasets (section 9.1 of the protocol).
  - The "Enrolled Set" will be renamed as the "All Study Participants" analysis set in the SAP and will include all study participants who sign the informed consent form.

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 2/3rd 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}, $t_{1/2}$, and $t_{1/2ss}$ 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 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}^2) – 1)] x 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 3 available measurements at a given time point, the mean will be calculated based on the number of measurements for which data are provided.

4.2.4 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: Calculation rules for duration of adverse eventsTable 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
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a participant in the FAS, 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.

FAS=full analysis set; PSL=padsevonil.

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/End-of-Treatment (EOT) visit will be assigned to the EOS/EOT Visit (Section 4.4) and analyzed accordingly as an EOS/EOT 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 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 participants

Not applicable.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

If PK effects by age group or gender are observed (i.e., between adult and elderly study participants) and if there are at least 5 participants within each subgroup category within the elderly age groups or gender groups based on the related subgroup analysis, then subgroup analyses may be performed.

An ANOVA with age group as the fixed effect and the primary PK parameters as the dependent variable will be performed. If the age group fixed effect is significant for at least one primary PK parameter at alpha = 0.1 significance level, then a subgroup analysis based on age group (≥65 to 74 years old and ≥75 years old) will be performed within the elderly cohort.

Similarly, an ANOVA with age group and gender as the fixed effects and the primary PK parameters as the dependent variable will be performed. If the gender fixed effect is significant for at least one primary PK parameter at alpha = 0.1 significance level, then a subgroup analysis based on gender (male and female) will be performed within both the adult and elderly cohorts.

5 STUDY POPULATION CHARACTERISTICS

5.1 Participant disposition

The number of participants who signed the informed consent, participants who completed or prematurely discontinued the study, as well as the reason for discontinuation will be summarized for all participants, based on the All Study Participants . A participant who completed the study is defined as a study participant who completed all visits up to and including the EOT/EOS visit (in the Follow-up Period).

The number and percentage of study participants who discontinued due to AEs will be summarized separately for all study participants and per age group (adults and elderly).

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

Screening failure reasons will be listed for the All Study Participants. A listing of participants who did not meet study eligibility criteria will also be presented for the All Study Participants.

In addition, the following listings will be presented:

- Participant disposition (All Study Participants)
- Study discontinuation (FAS)
- Visit dates (FAS)
- Participant analysis sets (All Study Participants)

The listing of participant disposition will include the date of informed consent, date and time of first and last dose of study medication, date of premature termination and primary reason (if applicable) and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and the number of days on study medication during the Period 1B (MD). During the Period 1A (SD), there was one day of study medication.

The number of days on study medication during the Period 1B (MD) will be calculated as follows:

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

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 for all participants based on the FAS and will include the deviation type and description. The number and percentage of participants in the FAS with IPDs will be summarized for all participants, per treatment period

(Period 1A, Period 1B, and whole treatment period) and for each deviation type. The denominator for the percentages will be the number of participants in the FAS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant (study participant) listing of demographics will be presented based on the ES. 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 for all participants based on the FAS. 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

Additionally, the categories will include:

- 18 to <65 years
- 65 to <75 years
- ≥75 years

Characteristics on experience of medical or psychiatric condition and on experience of procedures or surgeries will be also summarized for the FAS.

6.2 Other Baseline characteristics

Lifestyle information (alcohol, tobacco, caffeinated beverage and illicit drug use), psychiatric and mental status (orientation, attention, memory, mood and calculus) and suicidality risk evaluation (C-SSRS) at Baseline will be listed and summarized for all participants in the FAS.

6.3 Medical history, procedure history and concomitant medical procedures

Medical history will be listed and summarized (in an incidence table) for the FAS for all participants, by MedDRA system organ class (SOC) and preferred term (PT). 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.

Procedure history (procedures or surgeries prior to study entry) will be listed separately by the procedure reported term based on the FAS.

Concomitant medical procedures occurring during the study will be listed for the FAS.

6.4 Prior and concomitant medications

Prior and concomitant medications (Period 1A (SD), Period 1B (MD) and overall) will be listed and summarized for all participants in the FAS, 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. Separate tabulations will be presented for prior medications and concomitant medications (Period 1A (SD), Period 1B (MD) and overall). Prior medications which continued into the treatment period will also be classified as concomitant and will be included in both summaries. Concomitant medications (Period 1A (SD), Period 1B (MD) and overall) will be described for all participants and by age group based on the FAS.

All tabulations 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.

6.4.1 Prior medication definition

Prior medications include any medications that started prior to the date of first dose of PSL. This includes medications that started prior to the first dose of PSL and continued after.

6.4.2 Concomitant medication definition

SD-Concomitant medications are medications taken anytime during Period 1A (SD) (Day 1 to Day 7).

MD-Concomitant medications are medications taken anytime during Period 1B (MD) and through the Follow-Up Period (Day 8 to Day 22).

If a medication is started prior to PSL administration and stopped after the first PSL administration (SD period), then that medication will be classified as both prior and SD-concomitant medication. If this medication is stopped during the Period 1B (MD) or later, then that medication will also be classified as prior, SD-concomitant and MD-concomitant medication.

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.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

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

A Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis. Compliance with the study medication is defined as consumption by the study participant that confirms 100% with the planned dosage.

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

The calculation of the PK parameters of PSL and two of its metabolites [redacted]) will be performed by the Pharmacokinetic Pharmacodynamic Modeling and Simulation Department, ICON PLC. All PK TFLs will be produced by ICON PLC SAS programming (Early Phase).

Pharmacokinetic concentrations and PK parameters will be summarized using the PK-PPS and listed on the FAS by study participants. Figures of summaries will be based on the PK-PPS and figures of individual concentrations will be based on the FAS.

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

The plasma concentration-time profiles, urine amounts, and PK parameters of PSL and two metabolites of PSL [redacted] will be summarized by age group (adult [18-64 years] and elderly study participants [≥65 years]) and treatment period using descriptive statistics.

If PK effects by age group or gender as described in Section 4.10 observed, then the analysis of the primary PK variables will be repeated for subgroups within the adult and elderly cohorts.

Individual plasma PSL concentration-time profiles along with the individual plasma concentration-time profiles of the two metabolites of PSL will be displayed graphically on a linear-linear scale and semi-logarithmic scale (including spaghetti plots). Geometric mean plasma concentrations-time curves including 95% confidence intervals (CIs) will be displayed by cohort.

9.1 Analysis of the primary pharmacokinetic variables

Individual plasma concentrations of PSL will be listed and will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the

last dose of study medication (on Day 1 for Period 1A (SD) and on Day 16 for Period 1B (MD)). 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. The primary PK variables in plasma used for PSL are: C_{max}, AUC_{0-t}, AUC for the single dose (Period 1A) and $C_{max,ss}$, and AUC_{τ} for the multiple dose (Period 1B). C_{max} and $C_{max,ss}$ will be determined from the observed concentration and time data. AUC_{τ}, AUC and AUC_{0-t} will be computed using the linear up/log down trapezoidal rule.

The PK plasma concentrations and the primary PK parameters of PSL and its metabolites will be summarized by nominal sampling times 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 participant concentration-time profiles of PSL and its metabolites will be displayed graphically in linear and semi-logarithmic scale. Combined individual (spaghetti) plots will be displayed by age group and analyte with all participants overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of plasma concentrations for PSL over time will be presented, with all treatment group 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.

For the single dose (Period 1A) and multiple dose (Period 1B)) periods of the study, primary PK parameters (Single dose C_{max}, AUC_{0-t}, AUC and multiple dose: $C_{max,ss}$, AUC_{τ}) will be assessed in adults and elderly study participants with analysis of variance (ANOVA). Point estimates for the ratio of geometric means between adults and elderly study participants (and per category, if deemed necessary), and the respective 2-sided 90% CIs, will be computed using the least squares means and the root mean squares of error from the ANOVA of the log-transformed data with subsequent exponential transformation. Inter-participant variability on PK parameters will be derived from these analyses.

9.2 Analysis of secondary pharmacokinetic variables

The secondary PK variables are the amount excreted and metabolic ratio of amount excreted, measured in the urine PK of PSL and its metabolites. These PK variables along with urine concentrations and urine volume will be summarized for PSL and its metabolites by nominal sampling times 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]). Values below the LLOQ will be reported with a clear sign (flag variable in the dataset) indicating that they were below the LLOQ.

9.3 Analysis of other pharmacokinetic variables

The other PK parameters and their analysis are the following:

- The relationship between PK parameters (AUCt, AUC, AUC_{0-t}, CL/F , CL_R and $t_{1/2}$) of PSL and two metabolites of PSL and creatinine clearance, age (numerical), hepatic laboratory parameters (e.g., bilirubin, ALT, and AST) will be evaluated. The relationship will be displayed graphically using scatterplots, and the correlation between the PK parameter and the hepatic function test or age will be evaluated using linear regression, considering the PK parameter as the dependent variable and the hepatic function test or age as the independent variable.
- The point estimate and the 95% CI for the median differences for tmax between the adult and elderly cohorts will be computed according to the Hodges-Lehmann method.

10 SAFETY ANALYSES

All safety summaries and listings will be performed using the FAS. All safety variables will be summarized by the age group (adult and elderly study participants) and Treatment Period (SD, MD, and overall). Unless stated otherwise, all summaries including figures will be presented as detailed in the shells for figures. Summaries for continuous variables by time points will be based on the averaged value. Categorical variables will be summarized.

10.1 Extent of exposure

All study medication administration details will be listed by 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, SD-treatment-emergent and MD-treatment-emergent according to the intake of the study medication.

- Adverse events with a start date prior to the first dose of study medication will be defined as pre-treatment AEs.
- SD-treatment-emergent AE (SD-TEAE) is defined as any AE with a start date/time on or after the first dose of study medication and until Day 7 (last Day of Period 1A) or any unresolved event already present before administration of study medication that worsens in intensity following exposure to the SD-treatment.
- MD-treatment-emergent AE (MD-TEAE) is defined as any AE with a start date/time on or after the first dose of study medication during the Period 1 B (usually on Day 8) and until 168 hours after the last PSL intake or any unresolved event already present before

administration of study medication during Period 1B that worsens in intensity following exposure to the MD-treatment.

Where dates are missing or partially missing, AEs will be assumed to be SD-treatment-emergent and MD-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.

All AEs starting after the first intake of PSL through Day 7 will be attributed to SD-Treatment Emergent AEs; all AEs starting (strict) after Day 7 (the first PSL intake during Period 1B is foressen on Day 8) through Day 22 will be attributed to MD-Treatment Emergent AEs and AE starting more than 168 hours post last dose of PSL will be attributed to the FU period.

All AEs will be recorded in the Case Report form (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 drug PSL as judged by the Investigator.

The number and percentage of participants who experience SD-TEAEs and MD-TEAEs will be summarized by MedDRA SOC, PT. The occurrence and incidence of AEs will also be summarized by intensity and relationship to PSL. Adverse events leading to discontinuation and SAEs will also be summarized.

Summaries of TEAEs (SD-TEAEs and MD-TEAEs) will include the following:

- Incidence of TEAEs (overview including number and percentage of participants with any TEAEs, serious TEAEs, 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)
- Incidence of TEAEs
- Incidence of TEAE of special interest
- Incidence of TEAEs by relationship
- Incidence of TEAEs by maximum relationship
- Incidence of TEAEs by intensity
- Incidence of TEAEs by maximum intensity
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants
- Incidence of non-serious TEAEs above reporting threshold of 5% of participants by relationship

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

In summaries including relationship, the following relationships will be summarized: 'Not related', 'Related'. 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'. 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 participants and incidence of Non-Serious TEAEs above reporting threshold of 5% of participants by relationship 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 group 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 group column.A listing for all AEs will be presented by study participant and will include the onset date/time and outcome date/time of the event (including relative days), the AE duration (derived), time to onset (derived), pattern of event, intensity, relationship, action taken and outcome. In addition, the listing will flag AEs that led to discontinuation, TEAEs, AESIs and SAEs.

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 by age group and Treatment Period. Shift tables from Baseline to each post-Baseline time point will be presented by Treatment Period. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. Values outside the reference range for numeric variables will be flagged in the listings and in addition, will be listed separately. 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 i at 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.

Clinical chemistry and hematology parameters will be summarized by time point for both absolute values and changes from Baseline.

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 the following:

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

Figures of mean and mean change from Baseline may be presented for selected laboratory variables that will be identified at the DEM. Figures will be presented with all treatment periods included on the same plot.

Table 10-1: Laboratory measurements

Laboratory assessment	Parameters
Hematology	Hemoglobin[a], hematocrit, red blood cell count[a], mean corpuscular volume, platelets count[a], red blood cell indices consisting of mean corpuscular volume, mean corpuscular hemoglobin and reticulocytes, total white blood cell count, and differential consisting of absolute counts and percentages of the following leukocyte types: neutrophils[a], lymphocytes[a], monocytes, eosinophils, and basophils
Biochemistry	Sodium, potassium, calcium, glucose, blood urea nitrogen[a], creatinine[a], total and direct bilirubin (conjugated bilirubin when total bilirubin is outside the reference range), total protein, albumin, ALT[a], AST[a], and ALP[a]
Viral serology (only at Screening Visit)	HIV 1 and 2 Ab, HBsAg and HCV-Ab
Pregnancy (only at Screening Visit)	Serum pregnancy test (hCG)
Hormone tests (only at Screening Visit)	Follicle-stimulating hormone and estradiol (to confirm postmenopausal status in female study participants)
Urinalysis	Specific gravity, pH, glucose, protein, blood, leukocytes, nitrite, ketones, bilirubin, urobilinogen (with dipstick) If protein, blood, or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.

Laboratory assessment	Parameters
Drug screen	Amphetamines/methamphetamines, benzodiazepines, barbiturates, cocaine, cannabis, methadone, tricyclic antidepressants and opiates

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBsAG=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibodies; SFU=Safety Follow-Up

[a] Shift tables will be presented for these variables

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 after the Baseline Visit:

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

A by- participant listing of all vital sign measurements and change from Baseline will be presented at each time point.

Descriptive statistics will be reported for all vital sign measurements. Vital sign variables and changes from Baseline (pre-dose of each Treatment Period) will be summarized by descriptive statistics at each time point by age group and Treatment Period.

Figures of mean and mean change from Baseline will be displayed.

The number and percentage of study participants with treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) vital sign values as calculated by the criteria outlined in Table 10–2 will be summarized by the following age groups at each time point: Adults (18-64 years), Elderly (>=65-74 years), and Elderly (>= 75 years)

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

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 (time-matched Baseline on Day -1, when applicable) will be summarized using descriptive statistics by age group and treatment period 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:

- 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- participant listings. The listing will also include the change from Baseline (time-matched Baseline day of each treatment group, where applicable), based on the mean of the triplicate measurements at each time point, and will be presented by time point.

Measured values and changes from time-matched 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.

The following cut-points in QTcF (observed data and change from time-matched Baseline), 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 and mean change from Baseline will be displayed.

10.4.3 Other safety variables

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; Posner et al, 2011) data will be listed. 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

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

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

Treatment	Period 1A (SD)	Period 1B (MD)	All participants
Participant disposition			X
Protocol deviations			X
Demographics			X
Medical history			X
Lifestyle			X
Prior medications			X
Concomitant medications	X	X	X
Adverse Events	X	X	X
Laboratory tests	X	X	X
Other safety continuous measurements (vital signs, ECG)	X	X	X
Safety categorical results (laboratory shift tables, PDILI)	X	X	X
PK plasma and urine for PSL and metabolites	X	X	X

ECG=electrocardiogram; MD=multiple dose; PK=pharmacokinetic; PSL=Padsevonil; SD=single dose.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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