STATISTICAL ANALYSIS PLAN

Study: UP0056

Product: Padsevonil

AN OPEN-LABEL, PARALLEL-GROUP, PHARMACOKINETIC STUDY OF PADSEVONIL IN PARTICIPANTS WITH EITHER NORMAL HEPATIC FUNCTION OR WITH MODERATELY IMPAIRED HEPATIC FUNCTION (CHILD-PUGH CLASS B)

SAP/Amendment Number	Date
SAP Version 1.0	26-Nov-2019

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
Ae	Cumulative amount of PSL or its metabolite excreted in urine (Amount excreted)
ALT	alanine aminotransferase
ALQ	above the limit of quantification
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to the last quantifiable concentration
AUC_{0-12}	area under the curve from time 0 to 12h after a single PSL dose
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_{SS}/F	apparent total clearance at steady-state
CL_R	Renal clearance of PSL
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration at steady-state
C_{trough}	Measured concentration at the end of a dosing interval at steady state
CRF	case report form
CRU	clinical research unit

CSR	clinical study report
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
DEM	data evaluation meeting
ECG	electrocardiogram
EOS	End of Study
ETV	Early Termination Visit
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
IRN	International normalized ratio
IPD	important protocol deviation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MD	Multiple dose
MR_{Ae}	Metabolic ratio for Ae
MR_{AUC}	Metabolic ratio for AUC
$MR_{AUC\tau}$	Metabolic ratio for AUCτ

MR_{Cmax}	Metabolic ratio for C_{max}
$MR_{Cmax,ss}$	Metabolic ratio for $C_{max,ss}$
n	number of participants number of available observations
NCA	Noncompartmental analysis
PK Set	Pharmacokinetic 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 (C_{max} or $C_{max,ss}$)
t1/2	terminal elimination half-life
t1/2,ss	terminal elimination half-life at steady state
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of UP0056. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

This SAP is based on the following documents:

- Original protocol dated 02 July 2019, the protocol clarification memo 1 dated 19 July 2019 and the protocol clarification memo 2 dated 17 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 and endpoints

Table 2.1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the plasma PK of PSL in participants with moderate hepatic impairment and healthy study participants	• Single dose: C_{max}, AUC_{0-t}, AUC • Multiple dose: $C_{max,ss}$, AUC_{τ}
Secondary	
• To evaluate the safety and tolerability of PSL in participants with moderate hepatic impairment and healthy study participants	• Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation
Other	
• To evaluate the plasma PK of PSL and two of its metabolites ([redacted] and [redacted]) in participants with moderate hepatic impairment and healthy study participants	For the two PSL metabolites ([redacted] and [redacted]) • Single dose: AUC, AUC_{0-t}, and C_{max} • Multiple Dose: AUC_{τ} and $C_{max,ss}$

	For PSL and its metabolites • Single dose: t_{max}, t1/2, AUC_{0-12}, and metabolic ratios of AUC and C_{max} • Multiple dose: t_{max}, $t_{1/2}$, ss, C_{trough}, metabolic ratios of AUC_{τ} and $C_{max,ss}$ For PSL: • Single dose: CL/F • Multiple dose: CL_{ss}/F • Bound and unbound plasma concentration of PSL in 2 samples.
• To evaluate the urine PK of PSL and two of its metabolites ([redacted] and [redacted]) in participants with moderate hepatic impairment and healthy study participants	• For PSL: Amount excreted (Ae), CL_R and fe • For metabolites: Ae, metabolic ratio of amount excreted (MR_{Ae}), CL_R and fe_{met}
• To evaluate the safety and tolerability of PSL in participants with moderate hepatic impairment and healthy study participants	• 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 ECG assessment • Physical examination findings
BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic(s); PR=pulse rate; PSL=padsevonil; RR=respiratory rate; SAE=serious adverse event; TEAE=treatment-emergent adverse event	

2.2 Study design and conduct

This is a Phase 1, open-label study to evaluate the effect of moderate hepatic insufficiency on PK, safety, and tolerability following single and multiple oral doses of PSL. The study includes a total of up to 24 study participants (Cohort A [approximately 12 participants] healthy participants, and Cohort B [approximately 12 participants] participants with moderate hepatic impairment).

All cohorts will be initially matched for gender and then subsequently by weight to allow comparison across cohorts, if feasible. In each group there will be a homogenous repartition between male and female study participants with at least 2 study participants per gender.

A table of criteria to define Child-Pugh score along with classification for hepatic insufficiency is presented in Table 2-2. For those participants with hepatic insufficiency, only study participants classified as moderate, with a Child-Pugh score of 7 to 9 inclusive, will be enrolled.

The study utilizes a single dose (SD) and a multiple dose (MD) design. Screening of study participants will be up to 28 days prior to entry into the clinic. Prior to the start of the open-label, Single-Dose treatment period, the participants will check in to the clinic and complete Baseline procedures and assessments preceding the first administration of study medication. This will then be followed by a Washout Period before the start of a Multiple-Dose Treatment Period. A second Washout Period will be undertaken before the participants have their End of Study (EOS) Visit. Please see the Schedule of Activities (Table 2-3) for more specific details. Both healthy study participants and study participants with moderate hepatic impairment will take part in the Single Dose and Multiple Dose treatment periods.

The maximum total duration for the study participants is 46 days; it will consist of a Screening Period, Baseline, 2 Treatment Periods, 2 Washout Periods, and an EOS/ETV Visit.

Table 2.2: Criteria to determine Child-Pugh score

Measure	1 Point	2 Points	3 Points
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (sec prolonged), OR	<4	4 to 6	>6
INR (ratio)	<1.70	1.70 to 2.30	>2.30
Ascites	Absent	Slight	Moderate or participant is on medication(s) to control ascites
Hepatic encephalopathy	None	Grade 1 or 2	Grade 3 or 4 or participant is on medication(s) to prevent encephalopathy

Total points	Hepatic insufficiency classification
5 to 6	A-Mild
7 to 9	B-Moderate
10 to 15	C-Severe

INR=international normalized ratio

Table 2–3 Schedule of activities

		Single Dose					Multiple Dose						
Procedures	**Screening**	**Baseline**		**Treatment Period**	**Washout Period**		**Treatment Period**					**Washout Period**	**EOS[a] ETV**
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12**	**13 to 17**	**18**
Written informed consent	X												
Admit to clinic		X[b]	X										
Demographics and baseline characteristics	X		X										
Inclusion/Exclusion criteria verification	X		X										
General medical/medications/ procedures history	X		X										
Participant identification card assigned			X										
Determination of the Child-Pugh class	X												
Suicidality Risk Assessment (C-SSRS)[c]	X		X								X		X
Physical examination[d]	X		X								X		X
Psychiatric and mental status evaluation	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs[e]	X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[f]	X		X										X

Table 2-1: Schedule of activities

		Single Dose					Multiple Dose						
Procedures	**Screening**	**Baseline**		**Treatment**	**Washout Period**		**Treatment Period**					**Washout Period**	**EOS[a]** ETV
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12**	**13 to 17**	**18**
Determination of the prothrombin and INR values	X												
Hematology, serum chemistry, urinalysis[g]	X		X				X				X		X
Serology (HIV, HepB and HepC)	X												
12-lead ECG[h]	X		X	X			X	X	X	X	X		X
Urine and cotinine drug screen, and alcohol breath test	X		X										
Recording of adverse events/medical procedures	X		X	X	X	X	X	X	X	X	X	X	X
Administer PSL				X			X	X	X	X	X		
Study drug accountability				X			X	X	X	X	X		
Blood sampling for PSL PK levels[i]				X	X		X	X	X	X	X	X	
Additional blood sample PPB[j]											X		
Urine collection for PSL PK[k]				X	X						X		

Table 2-1: Schedule of activities

				Single Dose			Multiple Dose						
Procedures	**Screening**	**Baseline**		**Treatment Period**	**Washout Period**		**Treatment Period**					**Washout Period**	**EOS[a] ETV**
Study Days	**-28 to -3**	**-2**	**-1**	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12**	**13 to 17**	**18**
Discharge from clinic													X

CBC=complete blood count; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=End of Study; ETV=Early Termination Visit; h=hour(s); Hep B=hepatitis B; Hep C=hepatitis C; HIV=human immunodeficiency virus; INR=international normalized ratio; PK=pharmacokinetic; PPB=plasma protein binding; PSL=padsevonil; WOCBP=women of childbearing potential

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

[b] For convenience, the study participant may check-in to the clinic on the evening of Day -2. No study procedures will take place on Day -2. Study participants will be confined to the clinic from the time of check-in until check-out on Day 18.

[c] 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.

[d] Complete physical examinations will be performed on the days indicated. A brief physical examination will be conducted in a symptom-directed manner and only if clinically indicated (Section 8.4.1).

[e] Vital signs should be taken pre the morning dose of Padsevonil and around the same time as the ECGs, i.e. 3 hours post the morning dose.

[f] A serum pregnancy test will be performed for each WOCBP at Screening and a urine pregnancy test will be performed at any subsequent time points.

[g] Laboratory safety assessments (hematology, chemistry, and urinalysis) will be performed before the morning dose of PSL.

[h] 12-lead ECGs are taken 3 hours post the morning dose of Padsevonil . A 12-lead ECG will be performed after a rest of at least 5 minutes. All ECG recordings will be performed in triplicate and should be sufficiently separated so they have a different 'minute' on the timestamp, and all are done within 4 minutes.

[i] Pharmacokinetic blood samples will be taken at the following time points: Predose and 15 minutes, 30 minutes, 45 minutes, 1h, 1.5h, 3h, 4h, 5h, 6h, 8h, 12h, 24h (Day 2), 48h (Day 3), 72h (Day 4), and 96h (Day 5) postdose. On Days 8, 9, 10, and 11, PK samples will be taken at predose. On Day 12, PK blood samples will be taken at the following time points: predose and 15 minutes, 30 minutes, 45 minutes, 1h, 1.5h, 3h, 4h, 5h, 6h, 8h, 12h, 24h (Day 13), 48h (Day 14), 72h (Day 15), and 96h (Day 16) postdose.

[j] Two blood samples will be collected after multiple doses at steady state (Day 12 predose and 1.5h postdose [~t_{max}]) for PPB.

[k] Urine for PK assessment will be collected from all study participants on Day 1 at predose and from 0h to <12h and 12h to <24h, on Day 2 from 24h to <48h, on Day 3 from 48h to <72h, on Day 4 from 72h to <96h, (before the 8am cutoff on Day 5) postdose. Urine for PK assessment will also be collected from all study participants on Day 12 from 0h to <12h postdose.

2.3 Determination of sample size

No formal sample size calculation is required for a hepatic insufficiency study. Up to 24 study participants will be included with approximately 12 participants per cohort; this is considered sufficient to meet the study objectives.

Based on the FDA (FDA Guidance for Industry, 2003) regarding a two-fold change in AUC, exploratory sample size estimation was performed assuming the following:

- Log-normal distribution on AUC_{ss}
- Inter-study participant CV% of 40%
- Detection of a two-fold change in AUC_{ss}, which is equivalent to a 50% reduction in total body clearance

A sample size of 12 in each group will have >90% power to detect a fold change in means (expected ratio) of 2.000 assuming that the CV is 0.400 using a 2-sample t-test with a 0.050 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 UCB. The datasets will follow the UCB analysis data model (ADaM) data specifications. All statistical analyses will be performed using SAS® Version 9.4 or later (SAS Institute, Cary, NC, USA).

Pharmacokinetic parameters will be determined by non-compartmental analysis (NCA) with Pharsight Phoenix WinNonlin® v6.3 or higher (Certara L.P., Princeton, NJ, NCA) 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 and maximum. Geometric coefficient of variation (geoCV), geometric mean and 95% confidence interval (CI) for the geometric mean will also be presented in the descriptive statistics for the plasma concentration and PK parameters for PSL and two of its metabolites ([redacted] and [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 of its metabolites ([redacted] and [redacted]):

- n will be an integer
- Mean (arithmetic and geometric), standard deviation and median will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the original data
- Confidence intervals will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the value around which the confidence interval is constructed
- Coefficient of variation (CV) will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value
- If no 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 of its metabolites [redacted] and [redacted])), the following rules will apply regarding rounding and precision:

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

When reporting individual values and descriptive statistics for PK parameters (plasma and urine PK of PSL and two of its metabolites ([redacted] and [redacted] and metabolite to parent 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 cohort (healthy participants and participants with moderate hepatic impairment) and treatment period.

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), PSL, as reference.

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

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

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

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

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:

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

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 46 days with a maximum of 6 days exposure to investigational product, and will consist of the following periods:

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

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

- PSL Single Dose Administration Period (Day 1 to Day 7)

  In the Single Dose Period, study participants will receive a single oral dose of 100mg 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–). Days 2 to 7 are designated as a 6-day washout.

- PSL Multiple Dose Administration Period (Day 8 to Day 17)

  In the Multiple Dose Period, study participants will receive multiple oral PSL doses on Days 8 to 12, followed by a 5-day washout (Days 13 to 17). Padsevonil will be administered BID, with one 100mg dose in the morning [approximately 8:00am] and one 100mg dose in the evening [approximately 8:00pm] on Days 8 to 11. One dose of 100mg of PSL will be administered on the morning of Day 12. The Follow-Up Period consists of an End of Study (EOS)/Early Termination Visit (ETV) performed after discharge on Day 18 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 the Single Dose Period on Day 1. Scheduled or unscheduled measurements can be used as the Baseline value.

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

Variable	Baseline definition
Hematology, serum, chemistry, urinalysis	The baseline value is defined as the value on Day -1. If the baseline value is missing, the value obtained at Screening will be used.
Vital signs	The baseline value is defined as the value on predose on Day 1. If this value is missing, the last value prior dosing will be used.
ECG	12-lead ECG will be measured in triplicate. Baseline is the mean of the last three measurements on Day -1. 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. If the baseline value is missing, the value obtained at Screening will be used.

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

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

3.4 Protocol deviations

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

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

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

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

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

Additional DEMs may be conducted as deemed necessary.

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

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

3.5 Analysis sets

3.5.1 All Study Participants

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

3.5.2 Safety Analysis Set

The Safety Set (SS) consists of all study participants who received at least one dose of the investigational medicinal product (IMP). Study participants will be classified according to the treatment which was actually received. All safety analyses will be performed using the Safety Set.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) consists of all study participants who have received at least one dose of the IMP and have at least one valid post-baseline primary assessment observation. Study participants will be classified according to the treatment which was actually received.

3.5.4 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) 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 PKS.

3.6 Treatment assignment

Tables will be presented by cohort (Cohort A: Healthy Study Participants and Cohort B: Participants with Moderate Hepatic Impairment) and overall. Listings will be presented by study participants, cohort and study period as described in Section 3.2.2. PK summaries will be presented by treatment period (Single Dose and Multiple Dose), cohort and analyte (PSL and two of its metabolites).

A detailed schematic diagram of the study is provided in Table 3.1

Table 3–1: Padsevonil administration

Cohort A (Healthy Study Participants) and Cohort B (Child-Pugh Hepatic Insufficiency Classification of Moderate) (n=approximately 12 per cohort)											
	Single Dose			Multiple Dose							
	Treatment Period	Washout Period		Treatment Period						Washout Period	EOS/ETV
Day	**1**	**2 to 5**	**6 to 7**	**8**	**9**	**10**	**11**	**12 (AM)**	**12 (PM)**	**13 to 17**	**18**
PSL Dose (mg)	100 AM only			100 BID	100 BID	100 BID	100 BID	100 AM only			
Blood Sample	PK	PK (each day)		PK	PK	PK	PK	PK	PK	PK (until Day 17)	
Urine Sample	PK	PK (each day)						PK			

BID=twice daily; EOS=End of Study; ETV=Early Termination Visit; PK=pharmacokinetic; PSL=padsevonil

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 name of analysis datasets (section 9.1 of the protocol):

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

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

- Inclusion of a new analysis set: the Safety Set: The Safety Set was included in the SAP for the analysis of the safety parameters. The definition is given in section 3.5.1 of the SAP.

- Definition of Baseline for 12 lead ECG: The protocol states that the baseline ECG value will be the time-matched baseline day of each treatment period, when applicable. In the SAP, the ECG baseline value is defined as the mean of the last three predose measurements. If less than three predose replicates are available, the mean of the available predose replicates will be taken as the baseline.

- The data for the other endpoint "Bound and unbound plasma concentration of PSL in 2 samples" will not be available at the time of CSR/ Database lock and thus this will not be reported in the TFLs delivery. This will be addressed in a different report.

- Regarding the analysis of the vital signs, in the protocol, it is mentioned that frequency table of values outside the normal ranges will be produced by cohort and time points. This table will not be produced and is not mentioned in this SAP.

- For the two metabolites, the urine PK parameter, fe_{met}, has been specified.

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 2/3rd 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:

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

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

4.2.2 Safety laboratory data

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

4.2.3 Electrocardiogram data

For the 12-lead ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each time point. In the event that there are not 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- . Calculation rules for duration of adverse events can be found in Table 3- and will be applied for the calculation of duration of each AE. Adverse event duration is computed in and reported in day and time format: xx d hh:mm.

Table 3-2: 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.

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/Early Termination Visit (EOS/ETV) visit will be assigned to the EOS/ETV Visit (Section 4.4) and analyzed accordingly as an EOS/ETV 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/ETV 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

Not applicable

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 SS. A participant who completed the study is defined as a study participant who completed all visits up to and including the EOS/ETV visit (in the Follow-up Period). If there is more than one termination due to AE, then an additional table summarizing the discontinuations due to AE will be produced. In case that only one subject discontinues due to AE, then this will be presented in a listing.

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

Screening failure reasons will be listed for the All Study Participants.

In addition, the following listings will be presented:

- Participant disposition (All Study Participants)
- 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).

5.2 Protocol deviations

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

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant listing of demographics will be presented by cohort (Cohort A, Cohort B) based on All Study Participants. This will include the year of birth, age (in years), sex, race, ethnicity, country, height (in cm), weight (in kg) body mass index (BMI, in kg/m^2). The body weight will be the measurement obtained at Screening. Body mass index (kg/m^2) is documented in the CRF.

All demographic characteristics (except for year of birth) will be summarized by cohort and overall (Cohort A, Cohort B and All Study Participants) 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

6.2 Other Baseline characteristics

The criteria to determine the Child-Pugh score will be summarized for all participants by cohort and overall based on the FAS. This includes total serum bilirubin (mg/dL), serum albumin

(g/dL), prothrombin time (sec prolonged/international normalized ratio (INR)), ascites, hepatic encephalopathy, total points and hepatic insufficiency classification.

6.3 Medical history, procedure history and concomitant medical procedures

Medical history will be listed and summarized (in an incidence table) for the SS, 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.

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the date of first dose of PSL. Concomitant medications are medications taken after the first dose of PSL and/or the SFU Period. Concomitant medications will be attributed to the treatment period in which they start. Thus, any medication taken on Day 1 through Day 7 will be attributed to the Single Dose Period; any medications taken after the first dose of PSL on Day 8 through Day 18 (including SFU) will be attributed to the Multiple Dose Period.

If a medication starts prior to PSL administration and stopped after the first PSL administration or stopped during the Single Dose Period, then that medication will be classified as both prior and concomitant for Single Dose Period only. If a medication starts prior to PSL administration and is stopped during the Multiple Dose Period, then that medication will be classified as prior and concomitant for both Single and Multiple Dose Periods.

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

Prior and concomitant medications will be listed for all participants in the SS. Prior and concomitant medication will be tabulated separately. The summary will be presented by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Tabulation for prior medications will be presented by cohort; tabulation for concomitant medications will be summarized by treatment period and by cohort.

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.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Administration of PSL will be performed under the supervision of the Investigator (or designee) and the Investigator (or designee) will check the study participant's hands and the oral cavity immediately after dosing to confirm ingestion of the study medication. Compliance will be monitored by drug accountability and by drug assay for PSL (using the drug concentration in the blood/plasma). 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] and [redacted] will be performed by the Pharmacokinetics, Pharmacodynamics, Modeling and Simulation Department, [redacted]. All PK TFLs will be produced by [redacted] programming (Early Phase) or [redacted]

Pharmacokinetic concentrations and PK parameters of PSL and two of its metabolites ([redacted] and [redacted] will be summarized by treatment period (SD and MD) and cohort (healthy participants and participants with moderate hepatic impairment) based on the PKS.

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

Urine concentration of PSL and two of its metabolites ([redacted] and carboxylic acid [redacted]) and amount of PSL and two of its metabolites excreted will be listed by treatment period, cohort, and by study participant on the PKS.

9.1 Analysis of the primary pharmacokinetic variables

All deviations will be calculated relative to the last dose of study medication (on Day 1 for Single Dose Period and on Day 12 for Multiple Dose Period). Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly. The primary PK variables in plasma used for PSL are: C_{max}, AUC_{0-t} and AUC for the Single Dose Period and $C_{max,ss}$, and AUC_{τ} for the Multiple Dose Period. 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 will be summarized by period, cohort, and 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 will be displayed graphically in linear and semi-logarithmic scale. Combined individual (spaghetti) plots will be displayed by treatment period, cohort 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 cohorts overlaid on the same plot, in both linear and semi-logarithmic scale for each treatment period. 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 Cohort B only, the relationship between the primary PK parameters and the Child-Pugh parameters (total serum bilirubin, serum albumin, and prothrombin time (sec prolonged)) will be displayed graphically using scatter plots. This relationship will be evaluated further using linear regression, where PK parameter is the dependent variable and the Child-Pugh parameters are included as fixed effects. However, data from the linear regression analysis will be presented in a separate report.

For the Single and Multiple Dose Periods, primary PK parameters of PSL will be compared between the cohorts (healthy participants and participants with moderate hepatic impairment) using analysis of variance (ANOVA) as follows: point estimates for the ratio of geometric means between healthy participants and participants with moderate hepatic impairment 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. Interstudy participant variability of PK parameters will be derived from these analyses.

9.2 Analysis of secondary pharmacokinetic variables

No secondary pharmacokinetic variables will be analyzed in this trial.

9.3 Analysis of other pharmacokinetic variables

The other PK parameters for PSL metabolites ([redacted] and [redacted]) include:

- Single Dose Period: $AUC_{0-t,}$ AUC, $C_{max.}$, $t_{max,}$ $t_{1/2,}$, AUC_{0-12} , MR_{AUC} , MR_{Cmax}
- Multiple Dose Period: $C_{max,ss}$, $AUC_{\tau,}$, $t_{max,}$ $t_{1/2,ss}$, C_{trough} , $MR_{AUC\tau}$, $MR_{Cmax,ss}$

C_{max} and $C_{max,ss}$ will be determined from the observed concentration and time data. $AUC_{\tau,}$ AUC and AUC_{0-t} will be computed using the linear up/log down trapezoidal rule.

The other PK parameters for PSL include:

- Single Dose Period: CL/F, t_{max}, $t_{1/2}$, AUC_{0-12}
- Multiple Dose Period: CL_{SS}/F , t_{max}, $t_{1/2,ss}$, C_{trough} ,

- Bound and unbound plasma concentration of PSL will be analyzed in two samples. Results of analysis of bound and unbound plasma concentration of PSL will be presented in a different report, after final analysis will be provided.

CL/F and CL_{SS}/F will be determined from the observed concentration and time data.

The other PK parameters in urine of PSL and two of its metabolites ([redacted] and [redacted] are: Ae, CL_R, fe (PSL only), MR_{Ae} and fe_{met} (metabolites only).

The other PK parameters and the amount of urinary excretion of PSL and its metabolites will be summarized by treatment period, cohort and 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. t_{max}, $t_{1/2}$, and $t_{1/2ss}$ will only display the number of available observations [n], median, minimum, and maximum.

The point estimate and the 95% CI for the median differences for t_{max} between the 2 cohorts (healthy participants and participants with moderate hepatic impairment) will be computed according to the Hodges-Lehmann method.

10 SAFETY ANALYSES

All safety summaries and listings will be performed using the SS. Unless stated otherwise, all summaries including figures will be presented by treatment period, cohort (and overall), and time point. Summaries for continuous variables by time point will be based on the averaged value across cohort and treatment period.

10.1 Extent of exposure

All study medication administration details will be listed by cohort and study participant. The listing will include the date and time of administration of the morning and evening dose and total daily dose of medication.

Exposure data will be listed only.

10.2 Adverse events

All AEs will be coded using the MedDRA® and characterized as pre-treatment and treatment-emergent according to the intake of the study medication. Adverse events with a start date prior to the first dose of study medication will be defined as pre-treatment AEs. 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. Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of study medication. Missing or partially missing dates for AEs will be handled as described in Section 4.2.4.

Adverse events will be attributed to the treatment period in which they start. Thus, all AEs starting after the first intake of PSL through Day 7 will be attributed to Single Dose Period; all AEs starting after PSL intake on Day 8 though Day 18 will be attributed to the Multiple Dose Period and AEs starting more than 168 hours post last dose of PSL will attribute to the SFU 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 TEAEs will be summarized by MedDRA SOC, PT, treatment period and cohort.

Summaries of TEAEs will include the following:

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

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 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.

Listings of AEs and TEAES will include the following:

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

All listings (except incidence of all TEAEs) will be presented by study participant, treatment period and cohort and will include the onset date/time and outcome date/time of the event (including relative days), the event duration (derived), time to onset (derived), pattern of event, intensity, relationship, action taken, outcome and AEs that led to discontinuation. TEAEs and SAEs will be flagged.

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

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

10.3 Clinical laboratory evaluations

Laboratory data (clinical chemistry, hematology and urinalysis) and changes from Baseline (if applicable) will be summarized by descriptive statistics at each time point by cohort and treatment period for both absolute values and changes from Baseline. Shift tables from Baseline to each post-Baseline time point will be presented by cohort. 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 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.

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

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

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

Table 10-1: Safety Laboratory measurements

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="6">Hematology</td><td>Platelet Count</td><td rowspan="6">RBC Indices:
MCV
MCH
Reticulocytes</td><td rowspan="6">WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>RBC Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td>Coagulation panel</td></tr>
<tr><td>INR / Prothrombin</td></tr>
<tr><td rowspan="3">Clinical Chemistry[a]</td><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td></td></tr>
<tr><td>Routine Urinalysis[b]</td><td colspan="4">• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick. If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.</td></tr>
</table>

Other Screening Tests	• Follicle-stimulating hormone (at Screening only) to confirm postmenopausal status in female study participants • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Pregnancy test: Serum human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential) • Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab) The results of each test must be entered into the eCRF.

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

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

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

10.4.1 Vital signs

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

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

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

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 cohort and treatment period.

10.4.2 Electrocardiograms

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

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, based on the mean of the triplicate measurements at each time point, and will be presented by time point.

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

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

For observed data:

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

Absolute change from Baseline in QTcF:

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

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

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

Figures of mean change from Baseline in ECG parameters over time by cohort 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 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. This will be analyzed for the SS.

11 OTHER ANALYSES

A listing of comments will be presented.

12 REFERENCES

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

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13 APPENDICES

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

Treatment	Single Dose Period	Multiple Dose Period	All participants
Participant disposition	X	X	X
Protocol deviations	X	X	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 two of its metabolites	X	X	X

ECG=electrocardiogram; PK=pharmacokinetic; PSL=Padsevonil.

Approval Signatures

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