STATISTICAL ANALYSIS PLAN

Study: UP0083

Product: Padsevonil (UCB0942)

AN OPEN-LABEL, PARALLEL GROUP, SINGLE-CENTER STUDY TO INVESTIGATE THE PHARMACOKINETIC, SAFETY, AND TOLERABILITY PROFILES OF PADSEVONIL IN CYP2C19 GENOTYPED HEALTHY MALE JAPANESE STUDY PARTICIPANTS

PHASE 1

SAP/Amendment Number	Date
Final SAP	16 Dec 2019
Amendment 1	10 Feb 2020

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
BP	blood pressure
cBZR	central benzodiazepine receptor
CI	confidence interval
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
CPMP	Committee for Proprietary Medicinal Products
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic Case Report Form
EM	extensive metabolizer
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GABAA	gamma-aminobutyric acid type a receptor alpha1 subunit
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intermediate metabolizer
IMP	investigational medicinal product
IRB	Institutional Review Board
LF	linearity factor

MedDRA	Medical Dictionary for Regulatory Activities
m/p	Metabolite/parent
MTD	maximum tolerated dose
PDILI	potential drug-induced liver injury
PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per Protocol Set
PM	poor metabolizer
PS	Patient Safety
PSL	Padsevonil
PT	preferred term
QTc	QT interval corrected
QTcB	QT interval corrected for Bazett's formula
QTcF	QT interval corrected for Fridericia's formula
R_{AUC}	accumulation ratio based on AUC
R_{Cmax}	accumulation ratio based on C_{max}
$R_{m/p}$	accumulation ratio of m/p
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	single dose
SFU	Safety Follow-up
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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 UP0083 study. It also defines the summary tables, listings, and figures to be included in the final clinical study report (CSR) according to the protocol.

This SAP is based on, and assumes familiarity with, the following documents:

- Original Protocol (08 May 2019), Amendment 1 (22 Aug 2019)

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

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

UCB is the Sponsor and PAREXEL is the Contract Research Organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Objectives and endpoints

Objectives	**Endpoints**
Primary	
To evaluate the plasma PK of PSL in CYP2C19 genotyped healthy male Japanese study participants (extensive, intermediate, and poor metabolizers)	• Single dose: C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$ and t_{max} • Multiple-dose: $C_{max,ss}$, AUC_{τ}, $t_{1/2}$ and $t_{max,ss}$
Secondary	
To evaluate the safety and tolerability of PSL in healthy male Japanese study participants	Incidence of TEAEs
Other	

Objectives	Endpoints
To evaluate the plasma PK of PSL and its major metabolites [redacted]) in CYP2C19 genotyped healthy male Japanese study participants (extensive, intermediate, and poor metabolizers)	For PSL: • Single-dose: $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$ $AUC_{(0-12)}$ and CL/F • Multiple-dose: CL_{ss}/F, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, accumulation ratios based on AUC and C_{max} (R_{AUC} and R_{Cmax}) and linearity factor (LF) For PSL metabolites: • Single-dose: C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, t_{max}, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, $AUC_{(0-12)}$, and metabolite to parent ratios (m/p) based on C_{max} and AUC • Multiple-dose: $C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,ss}$, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, m/p based on $C_{max,ss}$ and AUC_{τ}, R_{Cmax}, R_{AUC} and accumulation ratio of m/p based on AUC ($R_{m/p}$)
To evaluate the urine PK of PSL and its major metabolites in CYP2C19 genotyped healthy male Japanese study participants (extensive, intermediate, and poor metabolizers)	For PSL and its metabolites: Single and Multiple-dose: A_e, f_e, CL_r Additional PK parameters of PSL metabolites (desmethyl and carboxy acid) in urine (CL_{form})
To evaluate the safety and tolerability of PSL in healthy male Japanese study participants	• Vital signs (PR, RR, SBP, DBP, and body temperature) • 12-lead ECG parameters • Physical examination findings • Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)

DBP=diastolic blood pressure; ECG=electrocardiogram; m/p=metabolite to parent ratio; PK=pharmacokinetics; PR=pulse rate; PSL=padsevonil; RR=respiratory rate; SBP=systolic blood pressure, TEAE=treatment-emergent adverse event.

2.2 Study design and conduct

This is a Phase 1, open-label, parallel group, single-center study to investigate the PK, safety, and tolerability profiles of PSL in CYP2C19 genotyped healthy male Japanese study participants.

The study consists of a Screening Period, a Single-dose Period, a Multiple-dose Period, and a Safety Follow up (SFU) Visit. The maximum total duration of the study is 49 days for each study participant, including the Screening Period (up to 28 days), the Single-dose Period (6 days, including Day -1 and PSL single-dose on Day 1 followed by a 4 day washout), the Multiple-dose

Period (9 days, including PSL dosing on Day 6 to 12 and study participants checkout of the center on Day 14), and the SFU Visit (maximum of 8 days after the last dose of PSL on Day 12).

The study participants will be examined for CYP2C19 genotyping (variant alleles: *2, *3, and *17) during the Screening Period and grouped as follows:

- Extensive metabolizers (*1/*1),
- Intermediate metabolizers (*1/*2, *1/*3),
- Poor metabolizers (*2/*2, *2/*3, *3/*3).

Other metabolizers who have the variant allele of *17 will be excluded from the study. Study participants will not be genotyped, if rescreened.

A total of 39 study participants (13 study participants per CYP2C19 genotype group) will be enrolled. If more than 2 study participants dropout in each group, additional study participants will be recruited at the discretion of the Investigator and Sponsor.

The schedule of activities is provided in Table 2-1.

Table 2-1: Schedule of activities

Study Period	Screening Period (28 days)	Single-dose Period						Multiple-dose Period									SFU Or Withdrawal Visit (maximum of 8 days after the last dose) [a]
Study Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Informed consent	X																
Inclusion/exclusion	X		X														
Body weight and height	X																
CYP2C19 genotyping	X																
Exploratory genotyping			X[n]														
Demographics, habits, lifestyle	X																
Medical/surgical history	X																
Concomitant medication/medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X	X														X	X
Psychiatric and mental status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X								X					X		X
Drug screen, ethanol breath test	X	X															
Serology (HBV, HCV, HIV, syphilis)	X																
Clinical laboratory tests	X	X					X								X		X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Period	Screening Period (28 days)	Single-dose Period						Multiple-dose Period									SFU Or Withdrawal Visit (maximum of 8 days after the last dose) [a]
12-lead ECG[d]	X		X	X				X	X	X	X	X	X	X	X		X
PSL administration			X[e]					X[f]	X[g]	X[g]	X[g]	X[h]	X[i]	X[i]			
PK blood sampling			X[j]	X[j]	X[j]							X[k]					
PK urine sampling			X[l]	X[l]	X[l]	X[l]	X[l]					X[m]					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stay in study center		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP2C19=cytochrome P450 family 2 subfamily C; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PK=pharmacokinetic; PSL=padsevonil; SFU=Safety Follow-up Visit

[a] The Safety Follow-up Visit will be performed 7 days (±1 day) after the last administration of PSL. Idem for the Withdrawal Visit, if applicable.

[b] A complete physical examination will be conducted at Screening and SFU. A brief physical examination will be conducted at all other visits, including at discharge.

[c] On dosing days, vital signs will be performed predose and 3 hours postdose. Blood pressure measurements will be performed in both supine and standing positions for orthostatic measurement at Screening (supine BP after the study participant has been lying down for 5 minutes and then standing BP after 1 minute and 3 minutes) and in a supine position for routine BP measurements at all assessments.

[d] 12-lead ECG will be performed after a rest of ≥5 minutes at Screening and at predose, 24 hours postdose, and at the SFU Visit. All ECG recordings will be performed in triplicate but no more than 2 to 3 minutes apart.

[e] PSL 200mg will be administered in the morning on Day 1 during the Single-dose Period.

[f] PSL 100mg will be administered in the morning and evening on Day 6 during the Multiple-dose Period.

[g] PSL 200mg will be administered in the morning and evening from Day 7 to Day 9 during the Multiple-dose Period.

[h] PSL 200mg and 100mg will be administered in the morning and evening, respectively, on Day 10 during the Multiple-dose Period.

[i] PSL 100mg will be administered in the morning and evening from Day 11 to Day 12 during the Multiple-dose Period.

[j] Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose.

[k] Predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the morning dose.

[l] Predose and 0 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 72 hours, and 72 to 96 hours postdose.

[m] 0 to 12 hours after the morning dose.

2.3 Determination of sample size

Considering the primary objective and based on UP0057 (with PSL 100mg BID), the inter participant CV of AUC_τ was estimated to be 39% (PSL). Using an inter-participant CV of 39%, a total sample size of 33 study participants (11 study participants per CYP2C19 genotype group) provides approximately 80% power for concluding that CYP2C19 genotype has no impact on the PK (using acceptance range of 0.5 to 2.0) based on expected ratio of 1.3 in PSL AUC_τ between CYP2C19 groups at a significance level of α=0.05.

In order to account for dropouts, the sample size will be increased by 20% (in total 39 study participants).

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by PAREXEL. The datasets will follow the UCB analysis data model (ADaM) data specifications.

All statistical analysis and generation of tables, figures, participant data listings, and statistical output will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA). The PK noncompartmental analysis (NCA) will be performed using Phoenix WinNonlin®v6.3 (or higher).

Continuous variables will be summarized by treatment period, visit and timepoint (where applicable) including number of participants (n), mean, standard deviation (SD), median, minimum, maximum and confidence intervals (CI) for the mean where stated in the SAP. Geometric coefficient of variation (geoCV), geometric mean and 95% CI for the geometric mean will also be presented in the descriptive statistics for the PK concentration data for PSL and its metabolites. 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):

- N will be an integer
- Mean, SD, and median will use 1 additional decimal place – compared to the original data
- Coefficient of variation (CV) (%) will be presented with one decimal place
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no participants have data at a given timepoint, 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 PK of PSL and PSL metabolites), the following rules will be applied:

- Individual values for PK concentration data will be reported to the same level of precision as the raw data received from the bioanalytical laboratory
- Minimum and maximum of PK concentration data will be reported using the same level of precision as the raw data
- Mean (arithmetic and geometric), median and SD will be reported using 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
- 95% CI for the geometric mean will use be reported using 1 additional decimal place compared to the value 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 PK of PSL and PSL metabolites), 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 SD and to 3 for the others

Categorical variables will be summarized by treatment period, visit and timepoint (where applicable) with frequency counts and percentages.

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

- For values where all participants fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is 0, there will be no percentage presented at all.
- All other percentage displays will use one decimal place.

Data listings containing all documented data and all derived data will be generated.

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

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

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 49 days with a maximum of 8 days exposure to PSL, and will consist of the following periods:

- Screening Period: Day -29 to Day -2
- Single-dose Period: Day -1 to Day 5
- Multiple-dose Period: Day 6 to Day 14
- SFU or Withdrawal Visit (maximum of 8 days after the last dose)

3.3 Definition of Baseline values

In general, Baseline will be the last non-missing assessment prior to dosing. The definition for each measurement is described below:

- Hematology, serum chemistry, urinalysis: Baseline is defined as Day -1. If Day -1 value is missing the Screening value will be used.
- Vital Signs: Baseline is defined as predose on Day 1. If predose on Day 1 is missing or multiple assessments occur, the last measure prior to dosing will be used.
- ECG: The mean of the last three measurements predose on Day 1 will be taken as Baseline. If there are less than three replicates at Day 1 predose, the mean of the available replicates (predose) will be taken as baseline.

3.4 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary PK outcome for an individual participant. Furthermore, participants will be excluded from the safety analysis only when there is documented evidence that they received no treatment. The criteria for identifying IPDs and the classification of IPDs will be defined within the protocol deviation specification document.

IPDs will include the following categories:

- Inclusion/exclusion criteria deviations
- Withdrawal criteria
- Prohibited concomitant medication use
- Incorrect treatment or dose

- Procedural non-compliance
- Visit schedule deviations
- Study drug administration deviations (including incorrect treatment received, handling and storage deviations and incorrect dosage received)
- Any vomiting episode(s) (that could impact PK concentrations)
- Missing data
- Other

All IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. After all data have been verified/coded/entered into a database, a data evaluation meeting (DEM) will be performed.

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

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

Additional DEMs may be conducted as deemed necessary.

The purpose of these DEM reviews will be to review all protocol deviations, define the analysis sets, and check the quality of the data. The reviews will also help decide how to manage problems in the 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 Enrolled Set

The Enrolled Set (ES) will consist of all participants who have signed an informed consent form for this study.

3.5.2 Safety Set

The Safety Set (SS) will consist of all enrolled participants who receive at least 1 dose of PSL.

3.5.3 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per Protocol Set (PK-PPS) will be a subset of the SS, consisting of those study participants who had no important protocol deviations affecting the PK parameters and for whom a sufficient number of samples are available to determine at least 1 PK parameter.

3.6 Treatment assignment and treatment groups

Unless stated otherwise, listings will be presented by study participant and genotype (Extensive, Intermediate and Poor Metabolizers), and summaries will be presented by treatment period (Single-dose Period and Multiple-dose Period) and genotype.

Study participants who meet all of the inclusion and none of the exclusion criteria will check into the study center on Day -1 (prior to the single dose [SD]). A SD of PSL 200mg will be administered in the morning on Day 1 of the Single-dose Period. During the Multiple-dose Period, PSL will be administered on the following dosage schedule:

- PSL 100mg twice a day (BID) on Day 6
- PSL 200mg BID from Day 7 to Day 9
- PSL 200mg in the morning on Day 10; PSL 100mg in the evening on Day 10
- PSL 100mg BID from Day 11 to Day 12

3.7 Center pooling strategy

The study is planned to be performed at a single 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 World Health Organization Drug Dictionary (WHODD). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

- The endpoint to evaluate the safety and tolerability of PSL in healthy male Japanese study participants has been changed from AEs to incidence of TEAEs to align with the summaries of interest
- The following PK parameters of PSL and its metabolites have been included for completeness: $AUC_{(0-12)}$, R_{AUC}, R_{Cmax}, LF and $R_{m/p}$ based on AUC (for metabolites only).

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. If a Baseline value is missing or not medically implausible, the last value before administration of PSL will serve as Baseline. Missing data for PK results and safety laboratory data will be handled as described in the sections below.

4.2.1 PK results

Measurements of plasma PK concentrations that are below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating the geometric mean and its 95% CI, the geometric CV, the arithmetic mean and SD for summaries and figures. Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LLOQ).

The following rules will apply for the summaries, listings and figures:

- If no participants have data, only "n=0" will be presented. The other descriptive statistics will be left blank.
- Descriptive statistics of plasma concentrations will be calculated if at most 1/3rd of the individual data points are missing or are not quantifiable (<LLOQ) at the given time-point. Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance. 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 the calculation of plasma PK parameters, all BLQ values occurring prior to C_{max} will be replaced by "0", except for embedded BLQ values (between two measurable data points) which will be treated as missing. Post-C_{max} BLQ values will be treated as missing. The Pharmacokinetic analysis will be performed in accordance to the User guide for Clinical Pharmacokinetics Modeling and Simulation version8 issued by UCB.
- The geometric CV will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

  Geometric CV (%) = sqrt[(exp (SD^2) – 1)] x 100

- The 95% CI for the geometric mean should be left blank if the SD is 0.
- For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements on Day 1 and Day 10, which will be imputed with zero for linear scale plots.
- Values below the LLOQ will be reported as BLQ in the listings.

4.2.2 Safety laboratory data

The rules for handling values that are BLQ 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 timepoint. In the event that there are not 3 available measurements at a given timepoint, the mean will be calculated based on the number of measurements for which data are provided.

4.2.4 Incomplete 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.

Partial start date

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 00:00 h
- 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 use the date of the first dose of study medication. 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 (ie, 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 use January 01 will be used. If time is missing this will be imputed as 00:00 h
- 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 (ie, event will be regarded as treatment-emergent)
- If the start date is completely unknown, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of Screening if this is later.

Missing start time

Missing start times will be imputed as 00:00h or with the time of dosing for events occurring on the date of administration of PSL.

Partial stop date

The following rules will be applied for 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

Calculation of duration of each AE when there being missing or partially missing date and/or time

Missing or partially missing dates and/or times will be imputed as described in Section 4.2.4. AE duration is computed and reported in day and time format: xx d hh:mm. Duration is not calculated when the outcome date is missing.

Table 4-1: Calculation rules for duration of adverse events			
Data availability	**Onset date/time**	**Outcome date/time**	**Calculation rules**
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a 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.

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 Early Withdrawal (EW) visit will be assigned to the EOS visit (Section 4.4) and analyzed accordingly as an EOS visit.

4.4 Handling of measurements obtained at the early withdrawal visit

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 7 to 7 days (+/- 1 day) after last intake of study medication and will then enter the SFU Period and will undergo the same assessments performed at the EOS Visit.

4.5 Interim analyses and data monitoring

No formal interim analyses are planned. Details about the safety analyses will be provided in the SMC Charter.

4.6 Multicenter studies

Not applicable.

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

A study participant is considered to have completed the study if he has completed all periods of the study including the last scheduled procedure shown in the Schedule of activities in the protocol.

The number and percentage of participants who were enrolled into the study, participants who completed or prematurely discontinued the study, as well as the reason for discontinuation will be summarized by genotype group and overall based on the SS.

The number and percentage of participants who discontinued due to AEs will be separately summarized by genotype group and overall based on the SS.

The number and percentage of participants included into each of the analysis sets will be summarized by genotype group and overall based on the ES. Percentages will be based on the ES for this summary.

Finally, screen failure reasons will be summarized by overall, based on the ES. A listing of participants who did not meet study eligibility criteria will also be presented.

In addition, the following listings will be presented:

- Participant disposition (ES)
- Study discontinuation (SS)
- Visit dates (SS)
- Participant analysis sets (ES)

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 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.

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

$$Number\ of\ days\ on\ study\ medication = Date\ of\ last\ dose\ received - Date\ of\ first\ dose\ received + 1$$

5.2 Protocol deviations

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

Any samples that are obtained outside the tolerance window permitted at the specified timepoint will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly.

A listing of all IPDs identified at the DEM will be presented by genotype group based on the SS and will include the deviation type and description. The number and percentage of participants in the SS with IPDs will be summarized by genotype group. The denominator for the percentages will be the number of participants in the SS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Description of the analysis of demographic and baseline characteristics of the participants is presented in this section. In listings, data will be presented typically sorted by participant number within each genotype group.

6.1 Demographics

All demographic characteristics obtained during the Screening Period will be summarized by genotype group and overall for the SS. This summary will include age (in years), sex (male), weight (kg), height (cm), body mass index (BMI in kg/m^2), race (Asian), ethnicity (Not Hispanic or Latino), ethnic subgroup (Japan) and CYP2C19 genotype.

The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for clinicaltrials.gov reporting (≤18, 19 to <65, and ≥65 years) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting (<18, 18 to <65, 65 to <85, and ≥85 years).

A by-participant listing of demographic characteristics as well as the date of birth will be presented for the ES.

6.2 Other Baseline characteristics

Lifestyle information (alcohol use, tobacco use, caffeinated beverage uses and illicit drug use) will be summarized by genotype group and overall for the SS and will be listed for the ES.

6.3 Medical history and concomitant diseases

Medical history will be listed and summarized (in an incidence table) for the SS 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 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 will be listed separately by the procedure reported term based on the SS. Concomitant medical procedures will be provided as a by-participant listing based on the reported term for SS.

6.4 Prior and concomitant medications

Prior and concomitant medications will be listed for SS, respectively, by WHODD Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3) and PT.

Tabulations will be presented for prior and concomitant medications separately where prior medications will be summarized by genotype and concomitant medications will be summarized by treatment period and genotype. Prior medications which continued into the treatment period will also be classified as concomitant and will be included in both summaries. The reported term will be included in the listing.

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 date of the first dose of PSL.

6.4.2 Concomitant medication definition

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 5 will be attributed to the Single-Dose Period; any medications taken after the first dose of PSL on Day 6 through Day 14 (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 4.2.1 in order to classify them as prior or concomitant.

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). 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 its metabolites [redacted] will be performed by the Quantitative Clinical Development Department, PAREXEL.

Pharmacokinetic concentrations and PK parameters will be summarized by treatment period (Single-dose and Multiple-dose) and genotype group (EM, IM and PM) using the PK-PPS and listed by treatment period, genotype and study participant using the SS. Figures of summaries will be based on the PK-PPS and figures of individual concentrations will be based on the SS.

Pharmacokinetic parameters of PSL and its metabolites will be calculated using the actual blood sampling times.

The primary plasma PK parameters for PSL include:

- Single-dose: C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, and t_{max}
- Multiple-dose: $C_{max,ss}$, AUC_{τ}, $t_{1/2}$, and $t_{max,ss}$

The other plasma PK parameters for PSL include:

- Single-dose: $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, $AUC_{(0-12)}$ and CL/F
- Multiple-dose: CL_{ss}/F, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, R_{AUC}, R_{Cmax}, and LF

The other plasma PK parameters for PSL metabolites include:

- Single-dose: C_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$, t_{max}, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, $AUC_{(0-12)}$ and m/p based on C_{max} and AUC

- Multiple-dose: $C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,ss}$, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, m/p based on $C_{max,ss}$ and AUC_{τ}, R_{AUC}, R_{Cmax}, and $R_{m/p}$ based on AUC

In addition, the PK parameters of PSL and its metabolites in urine after single and multiple-dose include: A_e, f_e, CL_r and CL_{form} (for PSL metabolites only).

9.1 Descriptive figures, Summaries and Listings

Individual plasma and urine concentrations of PSL will be listed separately by treatment period and genotype and will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the first dose (single-dose) or the last morning dose (multiple-dose) of study medication. 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 plasma concentration and the PK parameters (plasma and urine) of PSL and its metabolites will be summarized by treatment period, genotype and nominal sampling times using descriptive statistics (number of available observations [n], arithmetic mean, median, SD, 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.

The amount of urinary excretion of PSL (mg) per time interval after oral administration of PSL will be summarized by treatment period (SD: Day 1-5; MD: Day 10) and genotype using descriptive statistics.

Individual participant plasma concentration-time profiles of PSL and its metabolites will be displayed graphically overlaid on the same plot by treatment period in linear and semi-logarithmic scale.

Combined individual (spaghetti) plots for PSL and its metabolites will be displayed by treatment period and genotype with all participants overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of plasma concentrations for PSL and its metabolites over time will be presented, with genotype 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.

The following PK parameters of PSL and its metabolites will be graphically displayed (scatter plot, box plot) by genotype:

- Single-dose: PSL and metabolites: C_{max}, $AUC_{(0-t)}$, AUC, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, CL/F, A_e, f_e and CL_r; PSL metabolites: CL_{form} and m/p based on AUC
- Multiple-dose: PSL and metabolites: $C_{max,ss}$, AUC_{τ}, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, CL_{ss}/F, A_e, f_e, CL_r and R_{AUC}; PSL: LF; PSL metabolites: CL_{form}, m/p based on AUC and $R_{m/p}$ based on AUC

9.2 Statistical analysis of pharmacokinetics variables

The following PK parameters of PSL and its metabolites will be compared between genotype groups using analysis of variance (ANOVA) on the log-transformed parameters:

- Single-dose: PSL and metabolites: C_{max}, $AUC_{(0-t)}$, AUC, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, CL/F, A_e, f_e and CL_r; PSL metabolites: CL_{form} and m/p based on AUC
- Multiple-dose: PSL and metabolites: $C_{max,ss}$, AUC_{τ}, $C_{max,ss,bw}$, $AUC_{\tau,bw}$, CL_{ss}/F, A_e, f_e, CL_r and R_{AUC}; PSL: LF; PSL metabolites: $CL_{form,}$ m/p based on AUC and $R_{m/p}$ based on AUC

Point estimates for the ratio of geometric means and the respective 2 sided 90% CIs will be computed using the least squares means and the root mean squares of error, based on of the log-transformed data with subsequent exponential transformation.

The 3 comparisons of interest are the following (in sequential ordering):

- EM versus PM
- IM versus PM
- EM versus IM

The comparison "EM versus PM" will be firstly evaluated and then the 2 other comparisons against IMs will be performed only if the comparison EM versus PM is nonequivalent.

Interpretation of results will be performed by comparing the 90% CI interval of geometric mean ratio with the acceptance range of 50% to 200%.

9.3 Derivations of pharmacokinetic parameters

- AUC will be calculated as $AUC = AUC_{(0-t)} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable plasma concentration and λ_z is the apparent terminal elimination rate constant.
- $AUC_{(0-t)}$ will be calculated using the linear-up log-down trapezoidal rule. If single data points for plasma concentrations are missing, the parameter will be derived by interpolating with regard to the 2 neighboring non-missing concentrations.
- $t_{½}$ will be calculated as $\ln 2/\lambda_z$ where a simple linear regression (slope = $-\lambda_z$) of natural log (ln) concentration vs time for data points in the terminal phase of the concentration-time curve.
- Metabolite to parent ratio (m/p) based on C_{max} will be calculated using C_{max} of metabolite divided by C_{max} of parent (PSL) and $C_{max,ss}$ of metabolite divided by $C_{max,ss}$ of parent for single and multiple dose respectively.
- Metabolite to parent ratio (m/p) based on AUC will be calculated using AUC of metabolite divided by AUC of parent and AUC_{τ} of metabolite divided by AUC_{τ} of parent for single and multiple dose respectively.
- Body weight (BW) normalized parameters (ie, $C_{max,bw}$, $AUC_{(0-t),bw}$, $AUC_{,bw}$, $C_{max,ss,bw}$, and $AUC_{\tau,bw}$) will be calculated using the following formula where BW is measured on Day -1:

$$Parameter_{bw} = Parameter \times \frac{BW}{70}$$

- CL_r will be calculated as A_e/AUC and A_e/AUC_τ for single and multiple dosing respectively.
- f_e will be calculated as A_e/Dose for PSL and as (A_e of metabolite/Dose) x (molecular weight (MW) parent/MW metabolite) where the MW of PSL is 432.8, the MW of metabolite [redacted] is 419, the MW of metabolite [redacted].
- CL_{form} will be calculated as (A_e of metabolite/AUC of parent) x (MW parent/MW metabolite) for single-dose period and as (A_e of metabolite/AUC_τ of parent) x (MW parent/MW metabolite) for multiple-dose period.
- Accumulation ratio of C_{max} (RC_{max}) will be calculated using $C_{max,ss}$ following multiple dosing divided by C_{max} following a single dose for PSL and its metabolites.
- Accumulation ratio of AUC (RAUC) will be calculated using AUC_τ following multiple dosing divided by $AUC_{(0\text{-}12)}$ following a single dose for PSL and its metabolites.
- Accumulation ratio of m/p based on AUC (Rm/p) will be calculated using m/p [based on AUC] following multiple dosing divided by m/p [based on AUC] following a single dose.
- Linearity factor will be calculated using AUC_τ following multiple dosing divided by AUC following a single dose for PSL.

10 SAFETY ANALYSES

Safety analyses will be carried out in the SS unless otherwise stated. In listings, data will be presented by participant number and time point within each genotype group.

10.1 Extent of exposure

All study medication administration details will be listed by treatment period and participant. The listing will include the date and time of administration of the morning and evening dose, depending on the treatment period.

10.2 Adverse events

All Adverse events (AEs) will be coded using the MedDRA® and characterized as pretreatment and treatment emergent according to the intake of the study medication. AEs with a start date prior to the first dose of study medication will be defined as pretreatment AEs. A treatment emergent AE (TEAE) is defined as any AEs 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.

AEs will be attributed to the treatment period in which they start. Thus, all AEs starting after the first intake of PSL through Day 5 will be attributed to Single-Dose Period; all AEs starting after PSL intake on Day 6 will be attributed to the Multiple-Dose Period and AEs starting more than 168 hours post last dose of PSL will be attributed 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, genotype and by characterization according to the intake of PSL.

The occurrence and incidence of TEAEs will also be summarized by intensity and relationship to PSL. TEAEs leading to discontinuation and serious TEAEs will also be summarized by treatment group and by characterization according to the intake of PSL.

Summaries of TEAEs will include the following:

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

Summary tables will contain counts of study participant, percentages of study participants in parentheses and the number of events where applicable. A participant who has multiple events in the same SOC or 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.

Adverse event summaries will be ordered alphabetically by SOC and decreasing frequency of PT within SOC.

A listing for all AEs will be presented by participant, treatment period 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 and SAEs.

10.3 Clinical laboratory evaluations

Laboratory data and changes from baseline for numeric variables will be summarized and listed by genotype group, treatment period and across time. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. Values outside the reference range will be flagged in the listings, and in addition, will be listed separately. For the definition of Baseline values see Section 3.3.

A separate listing will present the participants who meet one or more of the following criteria at any treatment period or time point:

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

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

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

Clinical chemistry and hematology parameters will be summarized by genotype group, treatment period and timepoint 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 shift tables at all post- Baseline time points.

Table 10.1: Laboratory measurements

Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters		
Hematology [a]	Platelet Count	RBC Indices: MCV, MCH, % Reticulocytes	WBC Count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
	RBC Count		
	Hemoglobin		

Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
	Hematocrit			
Clinical Chemistry [a]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (unfasted)	Calcium	ALP	
Routine Urinalysis [a]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Drug screen (to include at minimum: amphetamines, cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV-1/2 Ab, HBsAg, HCV-Ab, syphilis) The results of each test must be entered into the eCRF.			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-1/2=human immunodeficiency virus-1/2; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; RBC=red blood cells; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cells
[a] Hematology, clinical chemistry, and urinalysis assessments will be performed under fasting conditions at Screening and non-fasting conditions at all other assessments.

The following additional laboratory variables will be listed separately:

- Serology (HBsAg, HCV-Ab, syphilis)
- Drug screen(amphetamines, cocaine, opiates, cannabinoids, and benzodiazepines)

10.4 Vital signs, Electrocardiograms, and other observations related to safety

10.4.1 Vital signs

The following vital sign measurements will be taken prior to blood sampling, where applicable.

- Systolic and diastolic blood pressure (mmHg)
- Pulse rate (beats per minute)
- Respiratory rate (breaths per minute)
- Body temperature (°C)

Descriptive statistics will be reported for all vital sign measurements in both standing and supine position. Observed results and changes from Baseline will be summarized by genotype group, treatment period and timepoint.

A by-participant listing of all vital sign measurements and change from Baseline will be presented by genotype group and timepoint.

The number and percentage of 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 vital sign variables and time point and will be presented by genotype group and overall.

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

Variable	Unit	Low[a]	High[a]
Systolic blood pressure	mmHg	Value <90 and/or ≥20 decrease from Baseline	Value >140 and/or ≥20 increase from Baseline
Diastolic blood pressure	mmHg	Value <50 and/or ≥15 decrease from Baseline	Value >90 and/or ≥15 increase from Baseline
Pulse rate	bpm	Value <45 and/or ≥15 decrease from Baseline	Value >90 and/or ≥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 will be summarized using descriptive statistics by treatment period, genotype and timepoint.

The following ECG parameters will be derived from digitally recorded 12-lead ECGs.

- Heart rate (HR) [beats per minute]
- RR interval [msec]
- PR interval [msec]
- QRS interval [msec]
- QT interval [msec]
- QTcF interval [msec]: QT interval corrected by Fridericia formula $QT_cF\ [msec] = \frac{QT\ [msec]}{\sqrt[3]{RR\ [sec]}}$

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 timepoint, and will be presented by treatment period, genotype group and timepoint.

Measured values and changes from Baseline will be summarized by treatment period, genotype group and timepoint (based on the mean of the triplicate values at each timepoint). Mean change

from Baseline in QTcF will be summarized by treatment period, genotype and timepoint and plotted over time by genotype. Figures will be presented with all treatment periods overlaid on the same plot by genotype.

In addition, the following cut-points in QTcF (raw data and change from Baseline) based on the mean of the triplicate data, will be summarized categorically (number and percentage of participants) by treatment period, genotype and timepoint.

For observed data:

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

For change from Baseline:

- <30msec
- ≥30 to <60msec
- ≥60msec

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

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

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 Suicidal risk monitoring

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 visits days where this questionnaire is collected.

11 OTHER ANALYSES

Not applicable.

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 PHARMACOMETRICS User Guide for Clinical Pharmacokinetics Modeling & Simulation. Version 8.0 – 04/JUL/12

13 APPENDICES

Not applicable.

14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

14.1 AMENDMENT 1

Rationale for the amendment

The SAP amendment is to accommodate the review comments to the dry run TFLs received from the Data Evaluation Meeting conducted on 28-Jan-2020.

Modifications and changes

Global changes

NA

Specific changes

- 4.2.1 PK results/ 1st and 2nd para

  The 95% CI lower and 95% CI upper should be left blank if the SD (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 SD for summaries and figures. Post t_{max}, BLQ values will be treated as missing 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 "LLOQ/2" for linear scale plots.

Has been changed to:

  Measurements of plasma PK concentrations that are below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating the geometric mean and its 95% CI, the geometric CV, the arithmetic mean and SD for summaries and figures. Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LLOQ).

- 4.2.1 PK results/ 3rd bullet

  For plasma concentrations,

Has been changed to:

  For the calculation of plasma PK parameters,

- 4.2.1 PK results/ 4th bullet

  On calculating the geometric mean and its 95% CI, the geometric CV, the arithmetic mean and SD, measurements of PK concentrations that are below the limit of quantification (BLQ) will be imputed with the numerical value of the LLOQ/2.

Has been changed to:

Removed.

- 4.2.1 PK results/ 7th bullet

  predose BLQ measurements on Day 10

Has been changed to:

predose BLQ measurements on Day 1 and Day 10

- 5.1 Participant disposition/ 2nd para

  the reason for discontinuation will be summarized by genotype group and overall based on the ES

Has been changed to:

the reason for discontinuation will be summarized by genotype group and overall based on the SS.

- 5.1 Participant disposition/ 5th para

  Finally, screen failure reasons will be summarized by genotype group and overall, based on the ES. A listing of participants who did not meet study eligibility criteria will also be presented by genotype group and overall.

Has been changed to:

Finally, screen failure reasons will be summarized by overall, based on the ES. A listing of participants who did not meet study eligibility criteria will also be presented.

- 6.1 Demographics/ 2nd para

  The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for clinicaltrials.gov reporting:

  · ≤18 years

  · 19 to <65 years

  · ≥65 years

Has been changed to:

The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for clinicaltrials.gov reporting: (≤18, 19 to <65, and ≥65 years) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting (<18, 18 to <65, 65 to <85, and ≥85 years).

- 9.3 Derivations of pharmacokinetic parameters / 2nd bullet

  AUC(0-t) will be calculated using the linear trapezoidal rule. If single data points for plasma concentrations are missing, the parameter will be derived by interpolating with regard to the 2 neighboring non-missing concentrations.

Has been changed to:

AUC(0-t) will be calculated using the linear-up log-down trapezoidal rule. If single data points for plasma concentrations are missing, the parameter will be derived by interpolating with regard to the 2 neighboring non-missing concentrations.

- 10.3 Clinical laboratory evaluations/ Last para

  Serology (HIV-1/2 Ab, HBsAg, HCV-Ab, syphilis)

Has been changed to:

Serology (HBsAg, HCV-Ab, syphilis)

15 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN

Not applicable.

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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Title: up0083 SAP Amendment 1

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Document Approvals	
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