# STATISTICAL ANALYSIS PLAN

## Study: UP0057

## Product: Padsevonil

## AN OPEN-LABEL, FIXED-SEQUENCE STUDY IN HEALTHY STUDY PARTICIPANTS TO EVALUATE THE EFFECT OF COADMINISTERED ERYTHROMYCIN ON THE PHARMACOKINETICS AND SAFETY OF PADSEVONIL

| SAP/Amendment Number | Date |
|---|---|
| Final SAP | 15 May 2018 |



**Confidentiality Statement**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADaM | analysis data model |
| Ae | cumulative amount of padsevonil or metabolites excreted into the urine |
| AE(s) | adverse event(s) |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ALQ | above the limit of quantification |
| AST | aspartate aminotransferase |
| AUCτ | area under the curve over a dosing interval (12 hrs) |
| $AUC_{(0-12)}$ | area under the plasma concentration-time curve from time zero to 12 hrs |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| CI | confidence interval |
| $CL_{form}$ | formation clearance of metabolites |
| $CL/F_{ss}$ | apparent total clearance at steady-state |
| CLr | renal clearance of padsevonil and its metabolites |
| $C_{max}$ | maximum observed plasma concentration |
| $C_{max,ss}$ | maximum observed steady-state plasma concentration |
| $C_{min}$ | minimum observed plasma concentration |
| $C_{trough}$ | predose observed plasma concentration |
| CRF | Case Report form |
| CRO | Contract Research Organization |
| CSR | clinical study report |

| | |
|---|---|
| CV | coefficient of variation |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DEM | data evaluation meeting |
| DDI | drug-drug interaction |
| ECG | electrocardiogram |
| EOS | End of Study |
| ES | Enrolled set |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| EW | early withdrawal |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| fe | fraction of padsevonil excreted into the urine |
| geoCV | geometric coefficient of variation |
| HBsAg | hepatitis B surface antigen |
| HCV-Ab | hepatitis C virus antibody |
| HIV-1/2Ab | human immunodeficiency virus-1/2 antibodies |
| ICF | Informed Consent form |
| ICH | International Council on Harmonisation |
| IMP | investigational medicinal product |
| IPD | important protocol deviation |
| $\lambda_z$ | apparent elimination rate constant |
| LLOQ | lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MW | molecular weight |

| | |
|---|---|
| n | number of subjects<br>number of available observations |
| NCS | noncompartmental analysis |
| PCS | potentially clinically significant |
| PDILI | potential drug-induced liver injury |
| PK-PPS | Pharmacokinetic-Per Protocol Set |
| PK | Pharmacokinetic(s) |
| PSL | Padsevonil |
| PT | preferred term |
| QTcB | QT corrected for heart rate using Bazett's formula |
| QTcF | QT corrected for heart rate using Fridericia's formula |
| SAE(s) | serious adverse event(s) |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SFU | Safety Follow-up |
| SOC | system organ class |
| $t_{½,ss}$ | apparent terminal elimination half-life at steady-state |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| TFLs | tables, figures and listings |
| $t_{max}$ | time to maximum concentration |
| 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 UP0057. 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, and assumes familiarity with, the following documents:

- Final protocol, dated 26 January 2018

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, A. et al. 2003).

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

# 2 PROTOCOL SUMMARY

## 2.1 Study objectives

### 2.1.1 Primary objective

The primary objective is to evaluate and compare the pharmacokinetics (PK) of padsevonil (PSL) in the presence and absence of erythromycin in healthy study participants.

### 2.1.2 Secondary objectives

The secondary objectives are to:

- Assess the safety and tolerability of PSL in the presence and absence of erythromycin in healthy study participants
- Evaluate and compare the plasma PK of PSL metabolites, [redacted] in the presence and absence of erythromycin in healthy study participants
- Assess and compare the urine PK of PSL and its metabolites [redacted] and [redacted]) in the presence and absence of erythromycin in healthy study participants

### 2.1.3 Exploratory objectives

The exploratory objectives are to:

- Estimate the inter- and intra-study participant variability in the plasma PK of PSL and its metabolites following administration of PSL in the presence and absence of erythromycin

- Evaluate and compare the venous blood and MITRA dried blood microsampling (dried blood) PK of PSL and its metabolite ([redacted] only) following administration of PSL in the presence and absence of erythromycin
- Archive blood samples for genotyping of drug metabolizing enzymes and biomarkers

## 2.2 Study variables

### 2.2.1 Pharmacokinetic variables

#### 2.2.1.1 Primary pharmacokinetic variables

The primary PK variables will comprise $C_{max}$ and $AUC_{(0-12)}$ following a single dose and $C_{max,ss}$ and $AUC_{\tau}$ following multiple doses of PSL in plasma:

- $C_{max}$: maximum observed plasma concentration
- $AUC_{(0-12)}$: area under the plasma concentration-time curve from time zero to 12 hours
- $C_{max,ss}$: maximum observed steady-state plasma concentration
- $AUC_{\tau}$: area under the curve over a dosing interval (12 hours)

#### 2.2.1.2 Secondary pharmacokinetic variables

The secondary PK variables for PSL will comprise $t_{max}$, and $C_{min}$ following single dose and $t_{max}$, $t_{½,ss}$, $\lambda_z$, $C_{trough}$, and $CL/F_{ss}$ following multiple doses, $C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$ for PSL metabolites [redacted], and the metabolite-to-parent ratios for $C_{max}$, $AUC_{(0-12)}$, and $AUC_{\tau}$ in plasma:

- $t_{max}$: time of maximum concentration
- $C_{min}$: minimum observed plasma concentration
- $t_{½,ss}$: apparent terminal elimination half-life at steady-state. The terminal half-life should be determined over a time interval equal to at least 2 x t½, using at least 3 datapoints. If the time interval is less than 2 x t½, the terminal half-life and all derived parameters (e.g. $CL/F_{ss}$) should be flagged.
- $\lambda_z$: apparent elimination rate constant
- $C_{trough}$: predose observed plasma concentration
- $CL/F_{ss}$: apparent total clearance at steady-state (for parent drug only).
- Metabolite-to-parent ratios calculated as: $C_{max}$ metabolite divided by $C_{max}$ of parent following a single dose, $C_{max,ss}$ metabolite divided by $C_{max,ss}$ of parent following multiple dosing. $AUC_{(0-12)}$ metabolite divided by $AUC_{(0-12)}$ parent following a single dose, $AUC_{\tau}$ metabolite divided by $AUC_{\tau}$ parent following multiple dosing.

Additionally, the secondary PK variables for PSL and its metabolites ([redacted], and [redacted]) will comprise $CL_r$, Ae, fe, and $CL_{form}$ in urine following a single dose and multiple doses:

- $CL_r$: renal clearance of PSL and its metabolites (only [redacted] and [redacted]) calculated as $Ae/AUC_{(0-12)}$ and $Ae/AUC_{\tau}$ for single and multiple dosing respectively.

- $A_e$: cumulative amount of PSL or metabolites excreted into the urine
- $f_e$: fraction of PSL or metabolites excreted into the urine calculated as Ae/Dose for PSL and as (Ae,met/Dose) x (molecular weight(MW)parent/MWmetabolite) where the MW of PSL is 432.8, the MW of metabolite [redacted] is 419, the MW of metabolite [redacted] is 433 and the MW of metabolite [redacted] is 595.
- $CL_{form}$: formation clearance of metabolites calculated as (Ae,met/$AUC_{(0-12)}$,parent) x (MWparent/MWmetabolite).

#### 2.2.1.3 Other pharmacokinetic variables

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

- Inter- and intra-study participant coefficients of variation (variability) in PK parameters for PSL and its metabolites
- The same PK parameters as listed in Sections 2.2.1.1and 2.2.1.2 for plasma data will be derived from venous blood with MITRA (dried blood) microsampling for PSL and its metabolite (only [redacted])

### 2.2.2 Safety variables

#### 2.2.2.1 Secondary safety variables

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

- Incidence of Adverse events (AEs) and Serious adverse events (SAEs)

#### 2.2.2.2 Other safety variables

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

- Changes in vital signs (pulse rate, blood pressure, respiratory rate, and body temperature)
- Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis)
- Changes in 12-lead electrocardiogram (ECG) assessments
- Physical examination (including neurological examination) findings

## 2.3 Study design and conduct

This is a Phase 1, open-label, drug-drug interaction (DDI) study designed to evaluate the effect of erythromycin on the PK and safety of PSL and its metabolites in a single cohort of 28 healthy study participants. The study uses a fixed-sequence multiple-dose design per recommendation for best practice (Liu et al, 2016). This study is planned to be conducted at a single site in the United Kingdom.

The total duration of study per study participant will be approximately 75 days with a maximum of 18 days exposure to PSL.

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

The study consists of 5 periods: A Screening Period, 3 Treatment Periods, and a Safety Follow-up (SFU) Period.

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 1, and a Baseline Visit, which will be conducted at the unit 1 day prior to Treatment Period 1.

Treatment Period 1 and Treatment Period 2 each consist of 5 days of treatment, followed by 1 week of wash-out.

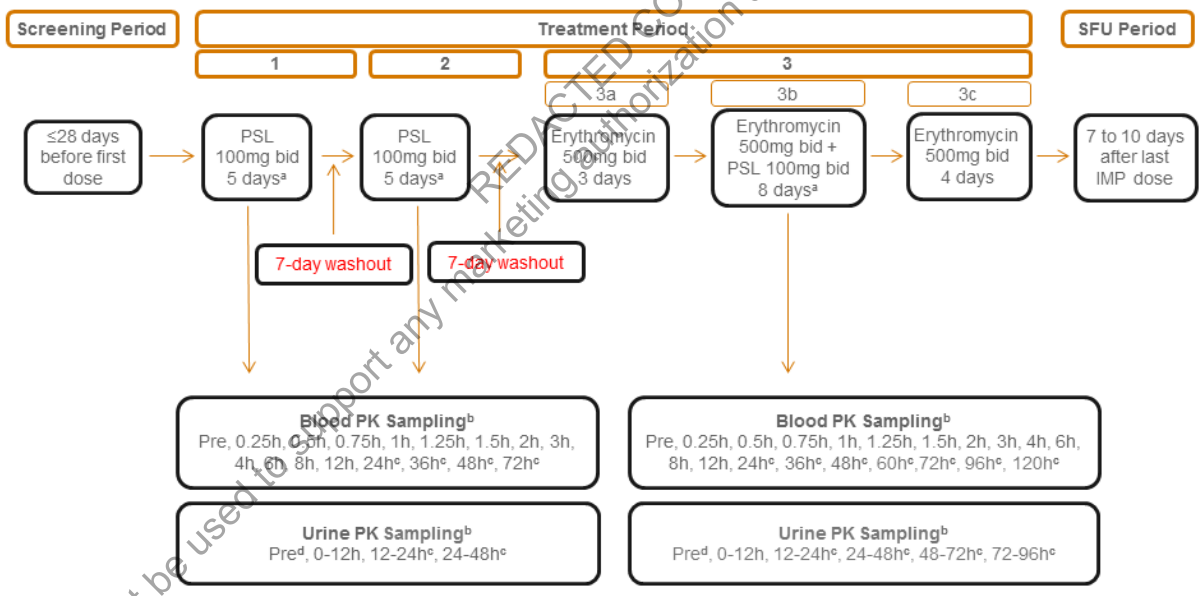
During Treatment Period 1 and Treatment Period 2, study participants will receive PSL 100mg bid for 4 days (Day 1 to Day 4 and Day 12 to Day 15). On the fifth day (Day 5 and Day 16), 100mg of PSL will be given as a single dose in the morning. Study participants then enter 1 week of wash-out (from the evening of Day 5 to Day 11 and evening of Day 16 to Day 22).

Treatment Period 3 consists of 2 erythromycin-only periods (Treatment Period 3a 500mg bid for 3 days and Treatment Period 3c 500mg bid for 4 days) and a combined PSL 100mg bid/erythromycin 500mg bid treatment period (Treatment Period 3b) for 8 days. Erythromycin and PSL will be administered concurrently in Treatment Period 3b.

The SFU Period consists of an End of Study (EOS) Visit performed 7 to 10 days after the final dose of erythromycin (Day 44 to Day 47) or upon discontinuation of the study.

The study schematic diagram for UP0057 is presented in Figure 2–1.

**Figure 2–1: Schematic diagram**




bid=twice daily; IMP=investigational medicinal product; PK=pharmacokinetic(s); PSL=padsevonil; SFU=Safety Follow-Up

[a] On the last day of Period 1, Period 2, and Period 3b, PSL will only be administered once in the morning.
[b] First and last PSL dose.
[c] Only after last PSL dose.
[d] Only after first PSL dose.

## 2.4 Determination of sample size

Using SimCYP simulations data, a sample size of 20 healthy study participants is needed to assess the PK interaction between PSL and erythromycin, and to estimate the mean PSL $AUC_{\tau}$ ratio of with/without erythromycin of 3.2 with a half-width of the confidence interval (CI) of 0.75.

This sample size has been evaluated with a conditional probability of 80%, assuming an inter-participant coefficient of variation of 140%, correlation of 0.5, 2-sided and $\alpha$=0.05.

A sufficient number of healthy study participants (up to 28) will be enrolled to have 20 completed 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 analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, United States). 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 subjects (n), mean, standard deviation (SD), median, minimum, maximum and confidence intervals for the mean where stated in the SAP. Geometric coefficient of variation (geoCV), geometric mean and 95% confidence interval (CI) for the geometric mean will also be presented in the descriptive statistics for the PK concentration data for PSL and its metabolites ([redacted] for both plasma conventional venous and MITRA dried blood sampling and [redacted] for venous sampling only). In all outputs the confidence limits will be restricted to the possible values that the variable can take.

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 subjects 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 (eg, 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 subjects in the respective analysis set and treatment period.

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

- n will be an integer

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

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

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 on or 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 subject data listing. In such cases, relative day should be presented as '--' in the relevant subject data listing.

### 3.2.2 Study periods

For each subject completing the study, the expected maximum duration of participation will be approximately 75 days with a maximum of 18 days exposure to PSL, and will consist of the following periods:

- Screening 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 1, and a Baseline Visit, which will be conducted at the unit 1 day prior to Treatment Period 1. Study participants will check-in at the unit on Day -2.

- Treatment Periods 1 and 2 (Day 1 to Day 11 and Day 12 to Day 22)

  Treatment Period 1 and Treatment Period 2 each consist of 5 days of treatment, followed by 1 week of wash-out. During Treatment Period 1 and Treatment Period 2, study participants will receive PSL 100mg bid for 4 days (Day 1 to Day 4 and Day 12 to Day 15). On the fifth day (Day 5 and Day 16), 100mg of PSL will be given as a single dose in the morning. Study participants then enter 1 week of wash-out (from the evening of Day 5 to Day 11 and evening of Day 16 to Day 22).

- Treatment Period 3 (Day 23 to Day 38)

  Treatment Period 3 consists of 2 erythromycin only periods (Treatment Period 3a and Treatment Period 3c) and a combined PSL/erythromycin treatment period (Treatment Period 3b). Study participants will receive erythromycin at the same clock-time PSL was administered in Treatment Period 1 and Treatment Period 2; erythromycin and PSL will be administered concurrently in Treatment Period 3b

  – Treatment Period 3a (Day 23 to 25)

    Study participants will receive erythromycin 500mg bid administered in the morning and in the evening.

  – Treatment Period 3b (Day 26 to 33)

Co-administration of PSL (100mg bid) and erythromycin (500mg bid) will begin on Day 26. Combination therapy will last for 8 days (Day 26 to Day 33). On Day 33, study participants will only receive a single dose of PSL 100mg in the morning, in addition to erythromycin 500mg bid.

– Treatment Period 3c (Day 34 to 38)

Study participants remain confined to the unit at the beginning of Treatment Period 3c. Study participants will receive erythromycin 500mg bid for the next 4 days (Day 34 to Day 37). Study participants will be discharged on Day 38 at the Investigator's discretion if no serious safety issues occur.

- The SFU Period, EOS visit (Day 44 to 47)

The SFU Period consists of EOS Visit performed 7 to 10 days after the final dose of erythromycin or upon discontinuation of the study.

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

## 3.3 Definition of Baseline values

In general, Baseline will be the last non-missing value prior to dosing. Scheduled or unscheduled measurements can be used as the Baseline value.

Measurement-specific Baseline timepoints are presented in Table 3–1.

**Table 3–1: Definition of Baseline**

| Measurement | Definition of Baseline |
|---|---|
| • Hematology, serum chemistry, urinalysis | Baseline or if missing the Screening value |
| • Vital signs | Predose for each treatment period.<br>Treatment Period 1 predose Day 1 or if missing Day -1. If Day -1 is missing the Screening value will be used.<br>Treatment Period 2 predose Day 12 or if missing predose Day 1<br>Treatment Period 3 predose Day 23 or if missing predose Treatment Period 1 value<br><br>Otherwise baseline = day -1 predose |

| Measurement | Definition of Baseline |
|---|---|
| • ECG | Time-matched predose for each treatment period.<br>Treatment Period 1 Day-1 Morning: predose, 1h, 2h, 3h, 6h similar "postdose" ; Evening: 0.5h "postdose"<br>Treatment Period 2 Day 11 Morning: predose, 1h, 2h, 3h, 6h similar "postdose" ; Evening: 0.5h "postdose"<br>Treatment Period 3a Day 22: Morning: predose, 1h, 2h, 3h, 6h similar "postdose" ; Evening: 0.5h "postdose"<br>Treatment Period 3b Day 25: Morning: predose, 1h,2h,3h, 6h similar "postdose" ; Evening: 0.5h "postdose"<br>Treatment Period 3c Day 33: Morning: predose, 1h,2h,3h, 6h similar "postdose" ; Evening: 0.5h "postdose"<br><br>Otherwise baseline = day -1 predose |

ECG=electrocardiogram; SFU=Safety Follow-Up.

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

12-lead ECG will be measured in triplicate with a 1-minute interval between replicates. Mean of the last three measurements predose will be taken as the baseline; if less than three replicates are available predose, the mean of the available replicates (predose) will be taken as the baseline. Time matched predose values are defined as the Baseline value (see Table 3-1).

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 value, as below:

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

The percentage change from Baseline to any subsequent post-Baseline visit will be calculated as follows:

$$100\ x(Post - Baseline\ Visit\ Value - Baseline\ Visit\ Value)/(Baseline\ Visit\ Value)$$

For 12-lead ECG, time-matched differences will only be calculated for the change from Baseline.

## 3.4 Protocol deviations

Important protocol deviations (IPD) are deviations from the protocol which potentially could have a meaningful impact on study conduct or the key safety and PK outcomes for an individual subject. The criteria for identifying such protocol deviations will be defined within the protocol deviation specifications document.

Important protocol deviations will include the following categories:

- Inclusion/exclusion criteria deviations
- Administration of prohibited concomitant medications
- Deviations relating to withdrawal criteria
- Visit schedule deviations

- Study drug administration deviations (including incorrect treatment received, handling and storage deviations and incorrect dosage received) and any vomiting episode(s) (that could impact PK concentrations)
- Procedural noncompliance
- Missing data

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 subjects' data (eg, missing values, withdrawals and protocol deviations).

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

## 3.5 Analysis sets

### 3.5.1 Enrolled Set

The Enrolled Set (ES) consists of all study participants who have signed the Informed Consent form (ICF).

### 3.5.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all study participants who have signed the ICF and received at least 1 dose of PSL. Analysis of this set will be according to the treatment the study participants actually received.

### 3.5.3 Pharmacokinetic-Per Protocol Set

The Pharmacokinetic-Per Protocol Set (PK-PPS) is a subset of the FAS, consisting of study participants who had no IPD 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 group

All subjects will complete the identical fixed-sequence multiple-dose treatments. Listings will be presented by subject and treatment period (Screening, Treatment Periods 1, 2, 3a, 3b and 3c, and SFU). Summaries will be presented by treatment (PSL, erythromycin, PSL + erythromycin and SFU), unless stated otherwise.

- PSL Treatment Period 1 and 2 (pooled data)
- Erythromycin Treatment Period 3a and 3c (pooled data)

- PSL + Erythromycin Treatment Period 3b
- SFU

Adverse events summaries will be presented by treatment within treatment periods as follows:

- Period 1 and 2: PSL
- Period 3a: Erythromycin (pre-PSL)
- Period 3b: PSL + Erythromycin
- Period 3c: Erythromycin (post-PSL)
- SFU

PK summaries will be presented as follows:

- PSL: Period 1
- PSL: Period 2
- PSL + Erythromycin: Period 3b

### 3.7 Center pooling strategy

Not applicable, this is a single center study.

### 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 protocol states that MITRA dried blood microsampling method will be compared to those of the plasma conventional venous sampling method using descriptive analysis (tables with summary statistics and graphs). Nonetheless, as described in Section 9.3, the exploratory analysis will also be described using linear mixed effects model.

## 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 SD (or equivalently, the geometric CV) is 0. Measurements of 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).

For all individual PK concentration figures any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ values (linear scale only) which will be imputed as zero.

The following rules will apply for PK data listings and summaries:

- Values below the LLOQ will be reported as (BLQ) in the listings
- 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 plasma concentrations, 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.
- For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements on Day 1, Day 12 and Day 23 for the treatment periods 1, 2 and 3 respectively, which will be imputed with zero for linear scale plots.
- If no subjects have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- The 95% CI for the geometric mean should be left blank if the SD (or equivalently, the geoCV) is 0.
- 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*

### 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 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 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 00:00 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 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 (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 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)

The following rules will be applied to partial stop dates:

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

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

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

| Data availability | Onset date/time | Outcome date/time | Calculation rules |
|---|---|---|---|
| Complete data | D1/T1 | D2/T2 | Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d |

| Table 4-1: Calculation rules for duration of adverse events | | | |
|---|---|---|---|
| **Data availability** | **Onset date/time** | **Outcome date/time** | **Calculation rules** |
| End time missing | D1/T1 | D2/-- | End time is substituted by time 23:59h (=23.98 in decimal format)<br>Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d |
| Start time missing | D1/-- | D2/T2 | Onset time is substituted by time 00:00h<br>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<br>For a subject in the FAS, D0 and T0 are the date and time of first administration of study medication and for screen failures, D0 is the date of the screening visit and T0 = 00:00h |
| End day and time missing | D1/T1 | --/-- | If the stop date is missing, duration will not be calculated. |
| Start and end date missing | --/-- | --/-- | If the stop date is missing, duration will not be calculated. |

FAS=full analysis set; PSL=Padsevonil.

## 4.3 Handling of repeated and unscheduled measurements

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

- For repeated measurements obtained prior to the first dose of study medication, the latest value (which may be scheduled or unscheduled) will be used in the calculation of the descriptive statistics
- For repeated measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of study medication
- Unscheduled and repeated measurements will not be used in the descriptive statistics at time points after first dose of study medication
- Unscheduled measurements performed for the 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

Subjects 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 10 days 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

Not applicable, there is no interim analysis and no data monitoring planned for this study.

### 4.6 Multicenter studies

Not applicable, this is a single center study.

### 4.7 Multiple comparisons/multiplicity

Not applicable.

### 4.8 Use of an efficacy subset of subjects

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 Subject disposition

The number of subjects who were enrolled into the study, subjects who completed or prematurely discontinued the study, as well as the reason for discontinuation, will be summarized for all subjects, based on the FAS. A subject who completed the study is defined as a subject who completed all visits up to and including the SFU.

The number and percentage of subjects who discontinued due to AEs will be summarized separately for all subjects, based on the FAS. This will be used for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting.

The number and percentage of subjects included in each of the analysis sets will be summarized for all subjects and for each treatment period based on the ES. Percentages will be calculated based on the FAS for the purpose of this summary.

Screen failure reasons will be summarized for the ES. A listing of subjects who did not meet study eligibility criteria will also be presented for the ES.

In addition, the following listings will be presented:

- Subject disposition (ES)
- Study discontinuation (FAS)
- Visit dates (FAS)
- Subject analysis sets (ES)

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

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

The number of days on study medicationwill be calculated as follows:

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

## 5.2 Protocol deviations

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

A listing of all IPDs identified at the DEM will be presented for all subjects based on the FAS and will include the deviation type and description. The number and percentage of subjects in the FAS with IPDs will be summarized for all subjects and for each treatment period for each deviation type. The denominator for the percentages will be the number of subjects in the FAS.

# 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

## 6.1 Demographics

A by-subject listing of demographics will be presented based on the ES. This will include the date of birth, age (in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI). The body weight will be the measurement obtained at Screening.

Body mass index in $kg/m^2$ is calculated based on the height (in m) and the weight (in kg) using the following formula:

$$BMI\ (kg/m^2) = weight\ (kg)/[height\ (m)]^2$$

The BMI will be reported to 1 decimal place.

All demographic characteristics (except for date of birth) will be summarized by for all subjects 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

Lifestyle information (alcohol, tobacco, illicit drug use and caffeinated beverage use) will be listed and summarized for all subjects in the FAS.

## 6.3 Medical history and concomitant diseases

Medical history will be listed and summarized (in an incidence table) for the FAS for all subjects, 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 subjects, and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the 'All Subjects' column.

Procedure history will be listed separately by the procedure reported term based on the FAS. Concomitant medical procedures occurring during the study will be listed for the FAS.

## 6.4 Prior and concomitant medications

Prior and concomitant medications will be listed and summarized for all subjects in the FAS, by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate tabulations will be presented for prior medications and concomitant medications. Prior medications which continued into the treatment period will also be classified as concomitant and will be included in both summaries. Concomitant medications will be described for all subjects and for each treatment period based on the FAS.

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

### 6.4.1 Prior medication definition

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

### 6.4.2 Concomitant medication definition

Concomitant medications are medications taken at least one day in common with the study IMP (after dosing with PSL) and/or the Safety Follow-Up Period.

If a medication is started prior to PSL administration and stopped after, that medication will be classified as both prior and concomitant

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

# 7 MEASUREMENTS OF TREATMENT COMPLIANCE

Administration of PSL or erythromycin 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] for both plasma conventional venous and MITRA dries blood and [redacted] for venous sampling only) will be performed by the Quantitative Clinical Development Department, PAREXEL. All PK TFLs will be produced by PAREXEL Biostatistics (Early Phase).

Pharmacokinetic concentrations and PK parameters will be summarized by treatment ie PSL with (Period 3b) and without erythromycin (Periods 1 and 2 separately), using the PK-PPS and listed on the FAS by treatment and subject. Figures of summaries will be based on the PK-PPS and figures of individual concentrations will be based on the FAS.

Pharmacokinetic parameters of PSL and metabolites ([redacted] for both plasma conventional venous and MITRA dried blood and [redacted] for venous sampling only) will be calculated using the actual blood sampling times.

## 9.1 Analysis of the primary pharmacokinetic variables

Individual plasma concentrations of PSL (from conventional venous sampling) will be listed by treatment period (PSL: Period 1; PSL: Period 2; PSL+ Erythromycin: Period 3b) and will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the first dose of study medication in that 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 are: $C_{max}$ and $AUC_{(0-12)}$ following a single dose and $C_{max,ss}$ and $AUC_{\tau}$ following multiple doses of PSL.

The PK plasma concentrations and primary PK parameters of PSL will be summarized by treatment period 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 indicating that they were below the LLOQ.

Individual subject 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 with all subjects overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of plasma concentrations for PSL over time will be presented, with all treatment periods 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 primary comparison of interest is the similarity of plasma PK parameters ($C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$) for PSL between treatment periods with erythromycin (Treatment Period 3b) and PSL without erythromycin (treatment periods 1 and 2). This will be assessed using a linear mixed effects model with treatment periods (1, 2 and 3b, comparing with vs without erythromycin periods) fitted as fixed effects and subject fitted as a random effect. The mixed effects model will be using Kenward-Rodgers degrees of freedom. Point estimates for the ratio of geometric means with and without erythromycin (Period 3b compared to periods 1 and 2) and the respective 2 sided 90% CIs will be computed using the least squares means and the root mean squares of error from the mixed effects model, based on of the log-transformed data with subsequent exponential transformation. In addition point estimates for the ratio of geometric means and the respective 2 sided 90% CIs will be presented for the following comparisons:

- Treatment Period 1 (PSL) compared to Treatment Period 3b (PSL + erythromycin)
- Treatment Period 2 (PSL) compared to Treatment Period 3b (PSL + erythromycin)

Treatment Period 1 (PSL) compared to Treatment Period 2 (PSL) Ping pong plots will be displayed for each of the PK parameters ($C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$) against treatment of PSL with (Treatment Period 3b) and without erythromycin (treatment periods 1 and 2, separately).

## 9.2 Analysis of secondary pharmacokinetic variables

The secondary PK variables in plasma for PSL are: $t_{max}$, and $C_{min}$ following single dose and $t_{max}$, $t_{½,ss}$, $\lambda_z$, $C_{trough}$, and $CL/F_{ss}$ following multiple doses, $C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$ for PSL metabolites ([redacted]), and the metabolite-to-parent ratios for $C_{max}$, $AUC_{(0-12)}$, and $AUC_{\tau}$.

Additionally, the secondary PK variables in urine for PSL and its metabolites ([redacted] and [redacted]) are: $CL_r$, Ae, $f_e$, and $CL_{form}$ in urine following a single dose and multiple doses.

Urine amount, time profiles and PK parameters of PSL and metabolites in urine will be summarized and plotted as described in Section 9.1. Urine concentration and amount excreted will be listed for PSL and the three metabolites.

Each of the secondary PK variables, for PSL and its metabolites in plasma, will be summarised by treatment period using the same descriptive statistics as for the plasma concentrations and PK variables in Section 9.1, and plotted in a similar manner.

The mixed effect model described in Section 9.1 will be applied for the PK variables $C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$ for the two PSL metabolites ([redacted]) in plasma (conventional venous of sampling). 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 from the mixed effects model, based on of the log-transformed

data with subsequent exponential transformation for the same comparisons than those described in Section 9.1.

## 9.3 Analysis of other pharmacokinetic variables

The other PK variables and their analysis are the followings:

- Inter- and intra-study participant coefficients of variation (variability) in PK parameters $C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$ for PSL and its metabolites

  Inter-study subject and intra-study subject variability on the PK parameters for PSL and its metabolites will be estimated from the mixed effects analysis described in Section 9.1. The point estimate (CV%) and 2-sided 90% CI for the inter-subject variability will be derived from the subject effect of the variance covariance matrix, and for the intra-subject variability, the point estimate (CV%) and 2-sided 90% CI will be derived from the residual effect of the variance-covariance matrix.

- Pharmacokinetic parameters $C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$ (and profile) data derived from MITRA dried blood concentration for PSL and its metabolite (only [redacted])
- The blood concentrations and blood PK variables for PSL and its metabolite based on the MITRA microsampling will be summarised and plotted as described in Section 9.1.
- As exploratory analysis, point estimates for the ratio of geometric means for the PK parameters $C_{max}$, $AUC_{(0-12)}$, $C_{max,ss}$, and $AUC_{\tau}$ for PSL based on the MITRA dried blood microsampling compared to the plasma conventional venous sampling along with the 2 sided 90% CIs will be computed using the least squares means and the root mean squares of error from a specific linear mixed effects model, based on of the log-transformed data with subsequent exponential transformation for the following periods:
  - Overall: conventional venous compared to MITRA
  - Period 1: conventional venous compared to MITRA
  - Period 2: conventional venous compared to MITRA
  - Period 3b: conventional venous compared to MITRA
- Scatter plots of the MITRA dried blood concentrations versus venous plasma concentrations for PSL and its metabolite will be presented. Furthermore a linear regression plot of the MITRA dried blood concentrations and venous plasma concentrations for PSL and its metabolite including the regression lines for the mean along with 90% confidence intervals will be presented for the log data.
- The predose trough concentrations for both plasma conventional venous and MITRA dried blood sampling methods obtained the Days 2 to 4, 13 to 15, and 27 to 33 will be listed separately. The trough PSL concentrations will be summarized by treatment period and day. Geometric mean along with their 95% CI for the trough concentrations will be plotted against time, with the 3 treatment periods overlaid in one figure (one plot for each sampling method).
- Erythromycin plasma concentrations may be listed if blood samples are bioanalyzed for erythromycin assessment.

# 10 SAFETY ANALYSES

All safety summaries and listings will be performed using the FAS. Unless stated otherwise, all summaries including figures will be by treatment period (Period 1 and Period 2 pooled, Period 3b, Period 3a and Period 3c pooled and EOS/SFU) as detailed in Table 13.1. Summaries for continuous variables by timepoint will be based on the averaged value across the pooled periods. Categorical variables will be summarized according to the actual period (no pooling).

## 10.1 Extent of exposure

All study medication administration details will be listed by treatment period and subject. The listing will include the date and time of administration of the morning and evening dose, depending on the treatment period, of either PSL and or erythromycin and total daily dose of both medications.

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 11 (before PSL on Day 12) will be attributed to Treatment Period 1 including the washout period Day 6 through Day 11. Likewise, all AEs starting after PSL on Day 12 until prior to erythromycin on Day 23 will be attributed to Treatment Period 2 including the washout period Day 17 through Day 22. There is no washout period between the Treatment Periods 3a, 3b and 3c. Adverse events with a start date after first dose of erythromycin in Treatment Period 3a until prior to the first dose of either PSL or erythromycin dose in Treatment Period 3b will be attributed to Treatment Period 3a and likewise for 3b and 3c. In Treatment Period 3c any AE starting more than 168 hours post last dose of erythromycin 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) as judged by the Investigator.

The number and percentage of subjects who experience TEAEs will be summarized by MedDRA SOC, PT, treatment period (Period 1 and Period 2 pooled, Period 3a, Period 3b, Period 3c and EOS/SFU) and treatment within treatment period (see Section 3.6). Summaries of TEAEs will include the following:

- Incidence of TEAEs (overview including number and percentage of subjects 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 non-serious TEAEs
- Incidence of TEAEs by relationship
- Incidence of TEAEs by maximum relationship
- Incidence of TEAEs by maximum intensity
- Incidence of fatal TEAEs by relationship
- Incidence of non-serious TEAEs by relationship
- Incidence of serious TEAEs by relationship
- Incidence of non-serious TEAEs above threshold of 5% of subjects in any treatment
- Incidence of non-serious TEAEs above threshold of 5% of subjects in any treatment by relationship

Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events where applicable. A subject who has multiple events in the same SOC and PT during a given treatment period will be counted only once in the subject counts for that treatment period but all events will be included.

In summaries including relationship, the following relationships will be summarized: 'Not related', 'Related'. Subjects 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'. Subjects 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 in the 'PSL+erythromycin' column for tables including event counts. For tables including only number and percentage of subjects, summaries will be ordered alphabetically by SOC and decreasing incidence of PT within SOC in the 'PSL+erythromycin' column.

A listing for all AEs will be presented by subject, 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 (clinical chemistry, hematology, and urinalysis) and changes from Baseline (if applicable) for numeric variables will be listed by subject, parameter, treatment period and timepoint. 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 subjects 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 subject, and will display all results obtained at that treatment period or time point for the specified variables.

A summary of subjects 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 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 timepoints.

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

- Serology
- Alcohol and cotinine drug screening, alcohol breath test
- Serum pregnancy test

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

**Table 10.1: Laboratory measurements**

| Laboratory assessment | Parameters |
|---|---|
| Hematology | Hemoglobin[a], hematocrit, red blood cell count[a], mean corpuscular volume, platelets[a], total white blood cell count, and differential consisting of absolute counts and percentages of the following leukocyte types: neutrophils[a], lymphocytes[a], monocytes, eosinophils, and basophils |
| Biochemistry | Sodium, potassium, calcium, inorganic phosphorous, glucose (fasting, only at Screening), urea[a], creatinine[a], total bilirubin (conjugated bilirubin when total bilirubin is outside the reference range), total protein, albumin, ALT[a], AST[a], and ALP[a] |
| Viral serology (only at Screening Visit) | HIV-1/2Ab, HBsAg and HCV-Ab |
| Pregnancy | Serum pregnancy test |
| Urinalysis | Specific gravity, pH, glucose (fasting, only at Screening), protein, blood, leukocytes, nitrite, ketones, bilirubin, urobilinogen (with dipstick)<br>If protein, blood, or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed. |
| Drug screen | Amphetamines/methamphetamines, benzodiazepines, barbiturates, cocaine, cannabis, methadone, tricyclic antidepressants and opiates |

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

[a] Shift tables will be presented for these variables

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

### 10.4.1 Vital signs

The following vital signs measurements will be obtained with the subject resting in the supine position for 10 minutes:

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

A by-subject listing of all vital sign measurements and change from Baseline will be presented by treatment period and timepoint.

Descriptive statistics will be reported for all vital sign measurements. Measured values and changes from Baseline will be summarized by vital signs variables and timepoint for each treatment period.

Figures of mean change from Baseline will be presented for each variable. Figures will be presented with all treatment periods overlaid on the same plot.

The number and percentage of subjects 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 treatment period at each timepoint and overall.

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

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

bpm=beats per minute; PCS=potentially clinically significant; TEMA=treatment-emergent markedly abnormal.
[a] Both conditions must be satisfied for a measurement to be considered potentially clinically significant.

### 10.4.2 Electrocardiograms

12-lead ECG will be recorded 3 times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The individual mean and change from baseline (time-matched Baseline day of each treatment period, when applicable) will be summarized using descriptive statistics by treatment period at each time point.

All standard 12-lead ECG recordings will be taken in triplicate with the subject resting in the supine position for at least 10 minutes. The following ECG parameters will be reported:

- PR interval
- QT interval
- QRS interval
- RR 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-subject listings. The listing will also include the change from Baseline (time-matched Baseline day of each treatment period, when applicable), based on the mean of the triplicate measurements at each timepoint, and will be presented by treatment period and timepoint.

Measured values and changes from time-matched Baseline will be summarized by treatment period and at each timepoint and by ECG variable (based on the mean of the triplicate values at each timepoint). The summaries will include the 2-sided 95% CIs. Mean change from time-matched Baseline in QTcF will be summarized and plotted over time. Figures will be presented with all treatment periods overlaid on the same plot.

The following cut-points in QTcF (observed data and change from time-matched Baseline), based on the mean of the triplicate data, will be summarized categorically (number and percentage of subjects) by treatment period at each timepoint.

For observed data:

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

Absolute change from Baseline in QTcF:

- <30msec
- ≥30 to <60msec
- ≥60 msec

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

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

#### 10.4.3.2 Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al, 2011) data will be listed. Module of the questionnaire, time point, question and the associated response will be listed for all the visits days where this questionnaire is collected.

## 11 OTHER ANALYSES

A listing of comments will be presented.

# 12 REFERENCES

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

Liu L, Bello A, Dresser MJ, Heald D, Komjathy SF, O'Mara E, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. J Clin Pharmacol. 2016;56 (2):143-51

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

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# 13 APPENDICES

## 13.1 Breakdown of treatment periods reported into the TFLs by study assessment data

### Table 13.1: Breakdown of treatment periods reported into the TFLs by study assessment data

| Treatment | PSL | | PSL | Erythromycin pre | PSL + Erythromycin | Erythromycin post | EOS/ SFU | All subjects |
|---|---|---|---|---|---|---|---|---|
| **Study Period** | **Period 1** | **Period 2** | **Period 1 + 2** | **Period 3a** | **Period 3b** | **Period 3c** | | |
| Subject disposition | X | X | | X | X | X | X | |
| Protocol deviations | X | X | | X | X | X | X | |
| Demographics | | | | | | | | X |
| Medical history | | | | | | | | X |
| Lifestyle | | | | | | | | X |
| Prior/ concomitant medications | | | | | | | | X |
| Adverse Events | | | X | X | X | X | X | |
| Laboratory tests | X | X | | | X | X | X | |
| Other safety continuous measurements (vital signs, ECG) | X | X | | X | X | X | X | |
| Safety categorical results (laboratory shift tables, PDILI) | X | X | | | X | X | | |
| PK plasma and urine for PSL and metabolites | X | X | | | X | | | |

ECG=electrocardiogram; EOS=end of study; PK=pharmacokinetic; PSL=Padsevonil; SFU=Safety Follow-up.
Note: Period refers to the treatment period.

# 14 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 SAP or amended SAP is released for execution.