FINAL ANALYSIS

STATISTICAL ANALYSIS PLAN

Study: UP0070

Product: Padsevonil

A MULTICENTER, OPEN-LABEL, PARALLEL-GROUP STUDY IN STUDY PARTICIPANTS WITH EPILEPSY TO EVALUATE THE EFFECT OF OXCARBAZEPINE ON THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF PADSEVONIL

SAP/Amendment Number	Date
SAP Version 1.0	26 Oct 2018

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LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
AED	antiepileptic drug
ALT	alanine aminotransferase
ALQ	above the limit of quantification
AST	aspartate aminotransferase
AUCτ	area under the curve over a dosing interval (12 hrs)
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BRV	brivaracetam
CI	confidence interval
CL/F_{ss}	apparent total clearance at steady-state
C_{max}	maximum observed plasma concentration
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
DEM	data evaluation meeting
ECG	electrocardiogram
EOS	End of Study
ES	Enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials

FAS	Full Analysis Set
FDA	Food and Drug Administration
geoCV	geometric coefficient of variation
ICF	Informed Consent form
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IPD	important protocol deviation
LEV	levetiracetam
LLOQ	lower limit of quantification
LTG	lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities
MHD	Mono Hydroxy Derivate
MW	Molecular Weight
n	number of subjects number of available observations
OXC	oxcarbazepine
PK-PPS	Pharmacokinetic-Per Protocol Set
PK	Pharmacokinetic(s)
PR	pulse rate
PSL	padsevonil
PT	preferred term
QTcF	QT corrected for heart rate using Fridericia's formula
RR	respiratory rate
SAE(s)	serious adverse event(s)

SAP	statistical analysis plan
SD	standard deviation
SFU	Safety Follow-up
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures and listings
t_{max}	time to maximum concentration
ULN	upper limit of normal
vs.	versus
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 UP0070. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

This SAP is based on the following documents:

- Final protocol, dated 08 June 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 et al, 2003).

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

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is to evaluate the effect of stable coadministered oxcarbazepine (OXC) (as monotherapy or adjunctive therapy) on the pharmacokinetics (PK) of padsevonil (PSL) in study participants with epilepsy compared with study participants co-medicated with stable doses of levetiracetam (LEV), lamotrigine (LTG), or brivaracetam (BRV) therapy.

2.1.2 Secondary objectives

The secondary objectives of this study are to:

- Evaluate the plasma concentrations of 10,11-dihydro-10-hydroxy-carbazepine (Mono Hydroxy Derivate [MHD]; circulating metabolite of OXC) before, during and after administration of repeated doses of PSL.
- Evaluate the effect of stable coadministered OXC (as monotherapy or adjunctive therapy) on the plasma PK of PSL metabolites, [redacted] and [redacted], in study participants with epilepsy compared with study participants co-medicated with stable doses of LEV, LTG or BRV therapy.
- Evaluate the safety and tolerability of PSL coadministered with stable OXC, LEV, LTG, or BRV therapy.

2.1.3 Exploratory objectives

The exploratory objectives of this study are to:

- Evaluate the plasma concentrations of LTG, LEV and BRV before, during and after administration of repeated doses of PSL. (Blood samples for plasma concentrations of LEV, LTG and BRV will be collected and stored during the study; they will only be measured on an as-needed basis.)
- Evaluate and compare the venous blood and MITRA microsampling (dried blood) PK of PSL following administration of PSL in study participants with epilepsy on stable coadministered OXC compared with study participants co-medicated with stable doses of LEV, LTG or BRV therapy.

2.2 Study variables

2.2.1 Pharmacokinetic variables

2.2.1.1 Primary pharmacokinetic variables

The primary PK variables will be C_{max}, t_{max}, AUC_{τ} and CL/F_{ss} obtained from the plasma concentration-time profiles for PSL:

- C_{max}: maximum observed plasma concentration
- t_{max}: time of maximum concentration
- AUC_{τ}: area under the curve over a dosing interval (12 hours)
- CL/F_{ss}: apparent total clearance at steady-state

2.2.1.2 Secondary pharmacokinetic variables

The secondary PK variable will be the trough plasma concentration of MHD (OXC metabolite) before, during and after dosing to steady state with PSL.
Additionally, secondary PK variables for PSL metabolites ([redacted] and [redacted]) will be C_{max}, t_{max}, AUC_{τ}, and the ratio of metabolite to PSL based on AUC_{τ}.

2.2.1.3 Other pharmacokinetic variables

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

- Trough plasma concentrations of LEV, LTG or BRV before, during and after dosing to steady state with PSL
- Plasma concentrations of PSL and metabolites in venous plasma and whole blood from MITRA microsampling (dried blood).

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 (PR), respiratory rate (RR), systolic blood pressure (SBP) and diastolic blood pressure (DBP))
- Changes in clinical laboratory test results (hematology, serum chemistry and urinalysis)
- Changes in 12-lead electrocardiogram (ECG) parameters
- Physical examination findings

2.3 Study design and conduct

This is a Phase 1, multicenter, open-label drug-drug interaction study in study participants with epilepsy, to evaluate the effect of OXC on the PK and safety and tolerability of PSL in 2 groups of 14 study participants each. A total of 28 participants will be evaluated in the following 2 groups:

- Group 1 (Inducers): study participants on stable therapy with OXC (at least 1200mg/day either as monotherapy or adjunctive to LEV, LTG, or BRV). Oxcarbazepine may be used as monotherapy (at least 7 study participants) or in combination with 1 or more of LEV, LTG, or BRV. (For adjunctive therapy, the dosing of each AED in the combination [OXC+LEV, OXC+BRV, or OXC+LTG] must be within the range used per label.)
- Group 2 (Neutral [control]): study participants on stable therapy with LTG (at least 150mg/day monotherapy or adjunctive to LEV or BRV), LEV (at least 1g/day monotherapy or adjunctive to LTG), or BRV (up to 200mg/day adjunctive to LTG). Lamotrigine or LEV may be used as monotherapy (at least 7 study participants) or in combination with each other. Brivaracetam may only be used in combination with LTG. (For adjunctive therapy, the dosing of each AED in the combination [LTG+LEV or LTG+BRV] must be within the range used per label.)

Padsevonil will be dosed to steady state (4.5 days) in both groups and the effect of background therapy on PSL PK will be assessed at steady state.

This study is planned to be conducted at sites in the Netherlands, Bulgaria and Germany (and potentially other countries in Europe).

The total duration of the study per study participant will be approximately 49 days (7 weeks) with a maximum of 12 days treatment period.

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 3 periods: up to 28 days for the Screening Period, 12 days for Treatment Period and up to 9 days for the Safety Follow-up (SFU) Period.

The Screening Period consists of a single Screening Visit, which will be conducted within 28 days prior to check-in for Treatment Period, and a Baseline Visit, which will be conducted one day prior to Treatment Period. A sufficient number of study participants with epilepsy will be screened to ensure that 14 study participants are included in each group.

The Treatment Period consists of 3 days of dose titration (Day 1, Day 2, and Day 3), 4.5 days of PSL maintained at a stable dose (Days 4 through 7 and the morning of Day 8), and 4.5 days of dose taper (evening of Day 8 and Days 9 through 12).

The dose titration will start with an initial PSL dose of 100mg, twice daily (BID) on Day 1 followed by 200mg BID for the following 2 days (Day 2 and Day 3). PSL 400mg will then be maintained by oral administration BID on Day 4 through 7 and one dose on the morning of Day 8.

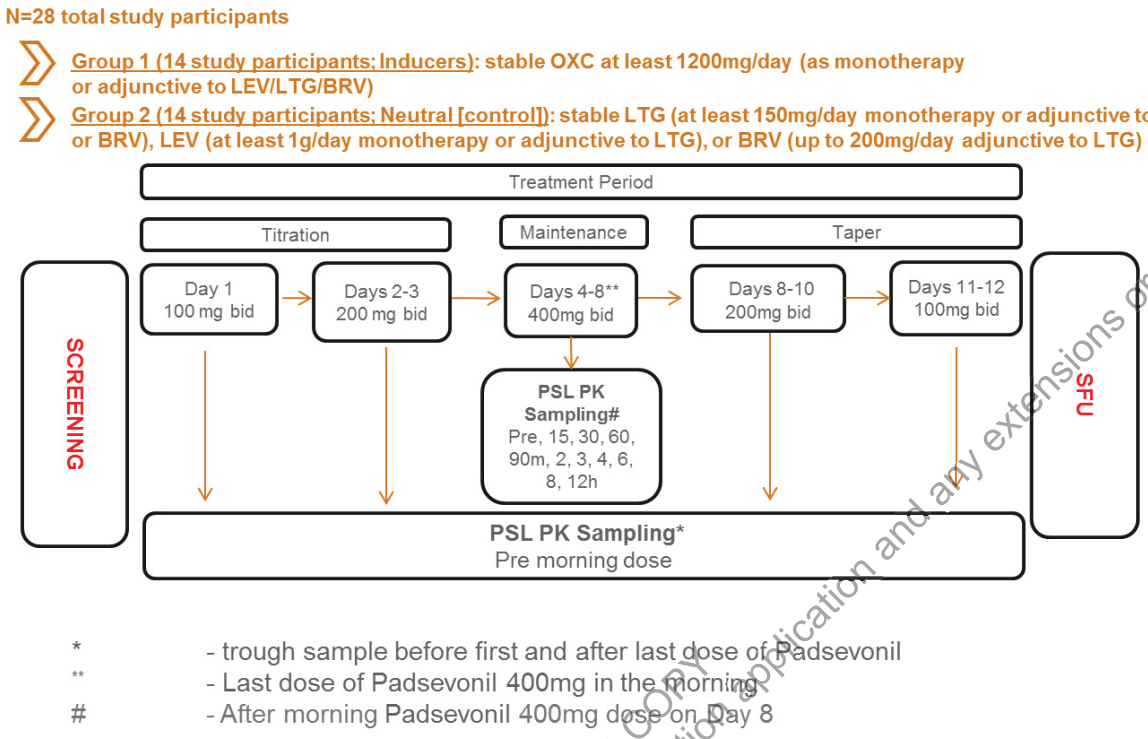
A dose taper will be initiated on the evening of Day 8, when study participants will be administered PSL 200mg. On Day 9 and Day 10, PSL 200mg BID will be administered. On Day 11 and Day 12, PSL 100mg BID will be administered.

The SFU Period consists of an End of Study (EOS) Visit performed on Day 20 ± 1 after discharged on Day 13 or upon discontinuation of the study (SFU period maximum of 9 days).

The study schematic diagram for UP0070 is presented in

Figure 2–1.

Figure 2–1: Schematic diagram



bid=twice daily; BRV=brivaracetam; LEV=levetiracetam; LTG=lamotrigine; OXC=oxcarbazepine PK=pharmacokinetic(s); PSL=padsevonil; SFU=Safety Follow-Up; T=Titration.

2.4 Determination of sample size

Considering the primary objective, and based on Study UP0002 (with PSL 400mg BID), the intersubject CV of AUC_τ was estimated to be 50% (PSL).

Using an intersubject CV of 50%, a power of 92% for the detection of a 43% decrease in AUC_τ of PSL with OXC vs. without OXC (1.75-fold change: ratio of larger mean vs. lower mean) at a significance level of α=0.05 (one-tailed test), the sample size calculation results in a total sample size of 28 study participants (14 study participants per groups). The sample size computation was performed using Nquery Advisor® version 7.0.

A total of 28 adult study participants with epilepsy (14 study participants in Group 1 [Inducers] and 14 study participants in Group 2 [Neutral {control}]) are planned for enrolment in this study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by ICON PLC. 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 (Certara L.P., Princeton, NJ, USA) for pharmacokinetics parameters estimation.

Continuous variables will be summarized by treatment group, visit and timepoint (where applicable) including number of subjects (n), mean, standard deviation (SD), median, minimum, maximum and 95% confidence intervals (CI) 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] and [redacted]), and PK parameters of PSL and metabolites. 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 group, visit and time point (where applicable) with frequency counts and percentages.

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

- For values where all study participants fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed
- All other percentage displays will use 1 decimal place

Percentages displayed based on continuous data (e.g. percentage changes from baseline) will be displayed to 1 decimal place. Unless otherwise stated, the denominator for the percentages will be based on the number of subjects in the respective analysis set and treatment group.

The MITRA samples will be obtained for Padsevonil and its metabolites only whereas venous plasma samples will be obtained for Padsevonil, its metabolites and the other antiepileptic drugs.

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] and [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 time point, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be left blank.

When reporting individual values and descriptive statistics for PK concentration data (plasma and blood [MITRA] PK of PSL and PSL metabolites, [redacted] and [redacted]), the following rules will apply regarding rounding and precision:

- Individual values for PK concentration data will be reported to the same level of precision as received from the bioanalytical laboratory
- Descriptive statistics for PK concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure– depending on the reporting format of the original data with a maximum of 3 significant digits - for the mean (arithmetic and geometric), median and 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] and [redacted]), and parent to metabolite ratio) the following rules will apply with regard to rounding and precision:

- Individual values for PK parameters will be reported to 3 significant figures
- Descriptive statistics for PK parameters should be rounded to 4 significant figures for the mean, median and 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 49 days with a maximum of 12 days exposure to investigational product, and will consist of the following periods:

- Screening Period (Day -28 to Day -2)

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

- Treatment Period (Day 1 to Day 12)

  The Treatment Period consists of 3 days of dose titration (Day 1, Day 2, and Day 3), 4.5 days of PSL maintained at a stable dose (Days 4 through 7 and the morning of Day 8), and 4.5 days of dose taper (evening of Day 8 and Days 9 through 12). Details are given in Table 3-2.

- The SFU Period consists of an End of Study (EOS) Visit performed on Day 20 ± 1 after discharged on Day 13 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 of treatment period. Treatment Period predose Day 1 or if missing Day -1. If Day -1 is missing the Screening value will be used. Otherwise baseline = Day -1 predose
• ECG	Time matched baseline at Day-1 at predose, 0.5h, 1h, 2h, 3h and 6h post morning dose of PSL on Day 1 and 0.5h predose of evening dose of PSL.
• C-SSRS	Separate baseline questionnaire for C-SSRS.

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

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

12-lead ECG will be measured in triplicate with a 2 to 3-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 visit value, as below:

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

3.4 Protocol deviations

Important protocol deviations (IPD) are deviations from the protocol which potentially could have a meaningful impact on study conduct or 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 investigational medicinal product (IMP). Analysis of this set will be according to the treatment the study participants actually received. All safety analyses will be performed using the FAS. All safety variables will be summarized by treatment.
Adverse Events will be displayed for all subjects including SF.

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 one PK parameter.

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

3.6 Treatment assignment and treatment group

All study participants will complete the different fixed-doses or combination multiple-dose treatments as per antiepileptic drugs (AEDs) treatment schedule including at least 7 days of monotherapy with AEDs. Padsevonil will be administered orally with 8oz (240 mL) water, 30 minutes after a light or standard meal for the morning dose and 30 minutes after a standard meal for the evening dose, according to Table 3-2. Listings will be presented by subject and treatment group (screening, treatment period and SFU). Summaries will be presented by treatment group (Group 1 (Inducer) and Group 2 (Neutral [control])), unless stated otherwise.

- PSL + OXC Group 1 (Inducer)
  PSL Group 2 (Neutral [control])

PK summaries will be presented as follows:

- PSL Treatment Period and SFU
- PSL + OXC Treatment Period and SFU
- LEV, LTG, BRV Screening, treatment period and SFU.

Table 3–2: Padsevonil administration

Day	Morning dose	Evening dose
1 (Ti1)	100mg	100mg
2 (Ti2)	200mg	200mg
3 (Ti3)	200mg	200mg
4-7 (M1-M4)	400mg	400mg
8 (M5/Ta1)	400mg	200mg
9 (Ta2)	200mg	200mg
10 (Ta3)	200mg	200mg
11 (Ta4)	100mg	100mg
12 (Ta5)	100mg	100mg

Abbreviations: M=Maintenance; Ta=Taper; Ti=Titration

3.7 Center pooling strategy

The data from the different centers will be pooled. The statistical analyses will not be performed by center.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version v 21.0). Medications will be coded according to the World Health Organization Drug Dictionary (WHODD) (Version SEP/2017). 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) 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. Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LLOQ).

For all individual PK concentration figures any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements which will be imputed with "LLOQ/2" for linear scale plots.

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 and dried blood concentrations will be calculated if more than 2/3rd of individual data points are 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 $t_{max,}$ only N, median, minimum and maximum will be displayed into the summary statistics,
- For plasma concentrations, all BLQ values occurring prior to t_{max} will be replaced by "LLOQ/2", except for embedded BLQ values (between two measurable data points) which will be treated as missing. Post-t_{max}, BLQ values will be treated as missing. The Pharmacokinetic analysis will be performed in accordance to the Guideline on performing NCA analysis dated 08 Nov 2017.
- For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements which will be imputed with "LLOQ/2" for linear scale plots.
- If no subjects have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- The geometric CV will be calculated using the following formula where SD 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 00:00h

- If only the month and year are specified and the month and year of the first dose of study medication is the same as the month and year of the start date, then the date of the first dose of study medication will be used. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of dosing then time will be imputed as the start time of the dosing (i.e., event will be regarded as treatment-emergent)
- If only the year is specified, and the year of the first dose of study medication is not the same as the year of the start date then January 01 will be used. If time is missing this will be imputed as 00:00h
- If only the year is specified, and the year of the first dose of study medication is the same as the year of the start date, then the date of the first dose of study medication will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of screening if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of first dose of study medication then time will be imputed as the start time of the study medication intake (i.e., event will be regarded as treatment-emergent)

The following rules will be applied to partial stop dates:

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

Missing or partially missing dates and/or times will be imputed as described in Table 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
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1

Table 4-1: Calculation rules for duration of adverse events			
Data availability	**Onset date/time**	**Outcome date/time**	**Calculation rules**
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a 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

Study participants who withdraw early from the study for any reason, including those withdrawn from study medication, will be asked to return for the EOS Visit 7 to 9 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.

4.6 Multicenter studies

This study is planned to be conducted at sites in Netherlands, Bulgaria and Germany (and potentially other countries in Europe). However, there is no plan to explore sites effect in the analysis.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of 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 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 for all participants, based on the ES. A participant who completed the study is defined as a study participant who completed all visits up to and including the SFU.

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

The number and percentage of study participants included in each of the analysis sets will be summarized for all participants and for each treatment group based on the ES. Percentages will be calculated based on the ES 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 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 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, for each treatment period and 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 (study participant) 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) body mass index (BMI, in kg/m^2). The body weight will be the measurement obtained at Screening.

Body mass index (kg/m^2) is 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 for all participants based on the FAS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years
- 19 to <65 years
- ≥65 years

Disease baseline characteristics will be also summarized for the FAS, including AED characteristics (name, dosage, frequency).

6.2 Other Baseline characteristics

Lifestyle information (alcohol, tobacco, illicit drug use and caffeinated beverage use), C-SSRS and Epilepsy characteristics (duration of epilepsy, seizure clusters history, status epilepticus history, seizure types) at Baseline will be listed and summarized for all participants 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 participants, by MedDRA system organ class (SOC) and preferred term (PT). The reported term will be included in the listing. The summary will include the number and percentage of study participant, 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 separately for AED and non AED medications, for all participants in the FAS, by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate tabulations will be presented for prior medications and concomitant medications. 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 participants and for each treatment group based on the FAS.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All 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 first dosing with PSL) and/or during 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 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] and [redacted] for both plasma conventional venous and MITRA dried blood) will be performed by the Quantitative Clinical Development Department, ICON PLC. All PK TFLs will be produced by ICON PLC SAS programming (Early Phase).

Pharmacokinetic concentrations and PK parameters will be summarized by treatment i.e. PSL with OXC (Group 1) and without OXC (Group 2), using the PK-PPS and listed on the FAS by treatment and study participants. Figures of summaries will be based on the PK-PPS and figures of individual concentrations will be based on the FAS.

Pharmacokinetic parameters of PSL and metabolites ([redacted] and [redacted] for both plasma conventional venous and MITRA dried blood) 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 and MITRA microsampling) will be listed by treatment group 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. Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly. The primary PK variables in plasma used for PSL and metabolites ([redacted] and [redacted]) are: C_{max}, t_{max}, and AUC_{τ}. In addition, CL/Fss will be evaluated for PSL only. C_{max} and t_{max} will be determined from the observed concentration and time data. When two or more identical peak concentrations are observed, t_{max} will be defined as the time of the first occurrence. AUC_{τ} will be computed using the linear trapezoidal rule.

The PK plasma and dried blood concentrations and the primary PK parameters of PSL and its metabolites from plasma and dried blood will be summarized by treatment group 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.

Individual participant concentration-time profiles of PSL, from conventional venous sampling and MITRA microsampling will be displayed graphically in linear and semi-logarithmic scale.

Combined individual (spaghetti) plots will be displayed by treatment group with all participants overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of plasma concentrations for PSL over time will be presented, with all treatment group overlaid on the same plot, in both linear and semi-logarithmic scale. For the linear scale plot only, the lower and upper 95% confidence interval (CI) for the geometric mean will be displayed.

All plasma concentration figures will include the LLOQ on the semi-logarithmic scale plots and will be based on scheduled times.

The primary comparison of interest is the similarity of plasma PK parameters (C_{max} and AUC_{τ}) for PSL between treatment group with OXC (Treatment Group 1) and PSL without OXC (Treatment Group 2). Pharmacokinetic parameters (C_{max} and AUC_{τ}) of PSL will be compared between the 2 treatment groups (Group 1 [Inducers] vs. Group 2 [Neutral {control}]) using analysis of variance (ANOVA) with treatment group fitted as fixed effects. Point estimates for the ratio of geometric means with and without OXC (Group 1 [Inducers] vs Group 2 [Neutral {control}])) 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 the log-transformed data with subsequent exponential transformation. Additional exploratory analyses may be conducted using subgroups of the 2 treatment groups (monotherapy subgroups, adjunctive subgroups).

9.2 Analysis of secondary pharmacokinetic variables

Pharmacokinetic parameters (Cmax, AUCτ) of PSL metabolites will be compared between the 2 treatment groups (Group 1 [Inducers] vs Group 2 [Neutral {control}]) using analysis of variance (ANOVA) on the log-transformed parameters.

The ANOVA model described in Section 9.1 will be applied for the PK variables (C_{max}, and AUC_{τ}) for the two PSL metabolites ([redacted] and [redacted]) in plasma (conventional venous 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 the log-transformed data with subsequent exponential transformation for the same comparisons than those described in Section 9.1.

Additionally, Cmax, tmax, AUCτ, for PSL metabolites ([redacted] and [redacted]) and the ratio of metabolite to PSL based on AUCτ will be summarized descriptively. Metabolite to parent ratios will be corrected for molecular weight. The molecular weight (MW) of PSL is 432.8, the MW of metabolite [redacted] is 419, the MW of metabolite [redacted] is 433. All secondary variables including trough plasma concentration of MHD (OXC metabolite) before, during, and after dosing to steady state with PSL will also be listed.

9.3 Analysis of other pharmacokinetic variables

The other PK parameters and their analysis are the following:

- The blood concentrations and blood PK variables for PSL and its metabolite based on the MITRA microsampling will be summarized and plotted as described in Section 9.1.

- The PSL concentrations and PK parameters obtained from MITRA microsampling method will be summarized as those obtained from the venous sampling method and compared with those of the conventional venous sampling method using descriptive analysis (tables with summary statistics and graphs).
- As exploratory analysis, point estimates for the ratio of geometric means for the PK parameters C_{max}, and AUC_{τ} for PSL based on the MITRA 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:
    - Overall: 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. The correlation between two measurements (conventional vs. MITRA) of PSL and its metabolites concentration will be evaluated using linear regression, considering conventional sample concentration as independent variable and MITRA sample concentration as dependent variable. Furthermore a Bland-Altman plot of the differences in concentration between MITRA dried blood and venous plasma vs. true measurement (average of MITRA dried blood with venous plasma) concentrations for PSL and its metabolite including regression line and its 90% confidence intervals will be presented for the log transformed data.
- The predose trough concentrations for both plasma conventional venous and MITRA dried blood sampling methods will be listed separately. The trough PSL concentrations will be summarized by treatment group and day. Geometric mean along with their 95% CI for the trough concentrations will be plotted against time.
- Trough plasma concentrations of LEV, LTG, or BRV before, during, and after dosing to steady state with PSL

10 SAFETY ANALYSES

All safety summaries and listings will be performed using the FAS. Unless stated otherwise, all summaries including figures will be presented by treatment group (Group 1 and Group 2) as detailed in the shells for figures (Table 13-1)Table 13-1. Summaries for continuous variables by timepoint will be based on the averaged value across the treatment group. Categorical variables will be summarized according to the actual group (no pooling).

10.1 Extent of exposure

All study medication administration details will be listed by treatment group and study participant. The listing will include the date and time of administration of the morning and evening dose, depending on the treatment group, (either PSL and/ or OXC) 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 group in which they start. Thus, all AEs starting after the first intake of PSL through Day 12 will be attributed to Treatment group AEs and AE 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, by treatment group and by characterization according to the intake of PSL. The occurrence and incidence of AEs will also be summarized by intensity and relationship to PSL. Adverse events leading to discontinuation and SAEs will also be summarized 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 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

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 and PT during a given treatment will be counted only once in the participant counts for that treatment group 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 in the group column for tables including event counts. For tables including only number and percentage of study participants, summaries will be ordered alphabetically by SOC and decreasing incidence of PT within SOC in the group column.

A listing for all AEs will be presented by study participant, treatment group 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 study participants, parameter, treatment group 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 study participant who meets one or more of the following criteria at any time point:

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

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

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

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

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

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

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

Figures of mean and mean change from Baseline may be presented for selected laboratory variables that will be identified at the DEM. Figures will be presented with all treatment periods 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 (only at Screening Visit)	Serum pregnancy test
Hormone tests (only at Screening Visit)	Follicle-stimulating hormone (to confirm postmenopausal status in female study participants)
Urinalysis	Specific gravity, pH, glucose, protein, blood, leukocytes, nitrite, ketones, bilirubin, urobilinogen (with dipstick) If protein, blood, or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.
Drug screen	Amphetamines/methamphetamines, benzodiazepines, barbiturates, cocaine, cannabis, methadone, tricyclic antidepressants and opiates

Laboratory assessment	Parameters

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

[a] Shift tables will be presented for these variables

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

10.4.1 Vital signs

The following vital signs measurements will be obtained with the study participants resting in the supine position for 10 minutes at all timepoint after the Baseline Visit:

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

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

The number and percentage of study participants with treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) vital sign values as calculated by the criteria outlined in Table 10–2 will be summarized by treatment group at each timepoint.

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

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

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

10.4.2 Electrocardiograms

12-lead ECG will be recorded 3 times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The individual mean and change from baseline (time-matched Baseline on Day -1 of each treatment, when applicable) will be summarized using descriptive statistics by treatment group 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 5 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- participant listings. The listing will also include the change from Baseline (time-matched Baseline day of each treatment group, where applicable), based on the mean of the triplicate measurements at each timepoint, and will be presented by treatment group and timepoint.

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

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

For observed data:

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

Absolute change from Baseline in QTcF:

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

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

Any incomplete triplicate measurements at a given 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 visit days where this questionnaire is collected.

11 OTHER ANALYSES

A listing of comments will be presented.

12 REFERENCES

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

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266-77.

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13 APPENDICES

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

Treatment	Group 1 (Inducers)	Group 2 (Neutral [control])	All subjects
Subject disposition	X	X	X
Protocol deviations	X	X	
Demographics			X
Medical history			X
Lifestyle			X
Prior medications			X
Concomitant medications	X	X	X
Adverse Events	X	X	
Laboratory tests	X	X	
Other safety continuous measurements (vital signs, ECG)	X	X	
Safety categorical results (laboratory shift tables, PDILI)	X	X	
PK plasma and dried blood for PSL and metabolites	X	X	

ECG=electrocardiogram; EOS=end of study; PK=pharmacokinetic; PSL=Padsevonil; SFU=Safety Follow-up.

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