A PHASE I, PHARMACOKINETICS, SAFETY AND TOLERABILITY STUDY OF SINGLE AND MULTIPLE ORAL DOSES OF SAFINAMIDE IN HEALTHY ADULT CHINESE VOLUNTEERS

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PAREXEL International

Zambon SpA

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Statistical Analysis Plan

Version: 1.0

PAREXEL Project Number: CCI

SPONSOR SIGNATURE PAGE

Approved by:

PPD

Zambon SpA

PAREXEL SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with CCI and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: PPD PPD Project Role: PPD

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	12 Dec 2018	New Document

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	AUC from time zero extrapolated to infinity
$AUC_{(0\text{-}t)}$	AUC from time zero to the last quantifiable concentration
$AUC_{(0\text{-}\tau),ss}$	AUC over the dosing interval at steady state
$AUC_{(0\text{-}24h)}$	AUC from time zero to 24h after administration
$AUC_{(0\text{-}24h),ss}$	AUC from time zero to 24h after administration at steady state
AUC%extrap	Percentage of AUCinf that is due to extrapolation beyond Tlast
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
$C_{avg,ss}$	Average concentration at steady state
CI	Confidence interval
C_{last}	Last quantifiable concentration at t_{last}
CL_R	Renal clearance
CL/F	Apparent clearance following oral administration
$CL/F_{,ss}$	Apparent clearance following oral administration at steady state
CRF	Case Report Form
CSP	Clinical Study Protocol
C_{max}	Maximum observed concentration
$C_{max,ss}$	Maximum observed concentration at steady state
C_{min}	Minimum observed concentration in the dosing interval
$C_{min,ss}$	Minimum observed concentration at steady state
CS	Clinically significant

Abbreviation / Acronym	Definition / Expansion
CV	Coefficient of variation
DBP	Diastolic blood pressure
DF%	Peak-trough fluctuation over one dosing interval at steady-state
DRM	Data Review Meeting
ECG	Electrocardiogram
ETV	Early termination visit
γ-GT	γ-Glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IMP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
$MRT_{(0\text{-}inf)}$	Mean residence time extrapolated to infinity
$MRT_{(0\text{-}inf),ss}$	Mean residence time at steady state extrapolated to infinity
NA	Not available
NCS	Not clinically significant
NK	Not known
OTC	Over the counter
PK	Pharmacokinetic
R_{acc}	Accumulation ratio
RBC	Red Blood Cells
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation / Acronym	Definition / Expansion
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error of the mean
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
$t_{½,ss}$	Apparent terminal elimination half-life at steady state
t_{last}	Time of last quantifiable concentration
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to occurrence of C_{max}
$t_{max,ss}$	Time corresponding to occurrence of $C_{max,ss}$ at steady state
V_z/F	Apparent volume of distribution during terminal phase
$V_z/F_{,ss}$	Apparent volume of distribution during terminal phase at steady state
WHO-DD	World Health Organisation - Drug Dictionary
K_{el}	Terminal elimination rate constant
$K_{el,ss}$	Terminal elimination rate constant at steady state
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-}inf)}$ obtained by extrapolation

1 INTRODUCTION

The present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations. Safinamide has been granted marketing authorization in EU (2015), US (2017) and Switzerland (2015).

In the present study, safinamide pharmacokinetic profile, safety and tolerability after single dose and at steady state will be investigated for the first time in Chinese healthy male and female volunteers.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 1.0 (December 10, 2018)

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate plasma safinamide pharmacokinetic parameters after single and multiple dose administration of the investigational medicinal products (IMP)

2.2 Secondary Objective

- To collect safety and tolerability data after single and multiple dose administration of the IMP

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Phase I, single center, single and multiple-dose, open-label, randomized, parallel-group, pharmacokinetics, safety and tolerability clinical study.

The study population will consist of 24 adult healthy male and female subjects (12 / cohort). Subjects will be randomized to two study cohorts to receive single and multiple doses of 50 mg safinamide (cohort 1), or single and multiple doses of 100 mg safinamide (cohort 2), according to the study randomized, parallel-group design, as follows:

Cohort	Period 1 - single dose Day 1	Washout	Period 2 - Multiple doses Days 8 - 14
Cohort 1	50 mg po	7 days	50 mg po o.d for 7 days
Cohort 2	100 mg po		100 mg po o.d. for 7 days

3.2 Endpoints and Associated Variables

3.2.1 Efficacy Variables

NA

3.2.2 Pharmacokinetic Variables

Unless otherwise stated, derivation of Pharmacokinetic (PK) parameters will be the responsibility of Qualitative Clinical Development (QCD), PAREXEL International. The following PK parameters will be determined for Investigational Medicinal Product (IMP) in plasma following single dose and multiple dose administration:

Table 1 Pharmacokinetic Parameters after Single Dose Administration

Parameter	Definition
C_{max}	Maximum observed concentration
t_{max}	Time corresponding to occurrence of C_{max}
$t_{½}$	Apparent terminal elimination half life
K_{el}	Terminal elimination rate constant
$AUC_{(0-t)}$	AUC from time zero to the last quantifiable concentration
$AUC_{(0-inf)}$	AUC from time zero extrapolated to infinity
$\%AUC_{ex}$	Percentage of $AUC_{(0-inf)}$ obtained by extrapolation
CL/F	Apparent clearance following oral administration
V_z/F	Apparent volume of distribution during terminal phase

Table 2 Pharmacokinetic Parameters after Multiple Dose Administration

Parameter	Definition
$C_{max,ss}$	Maximum observed concentration at steady state
$C_{min,ss}$	Minimum observed concentration at steady state
$t_{max,ss}$	Time corresponding to occurrence of $C_{max,ss}$ at steady state
$t_{½,ss}$	Apparent terminal elimination half-life at steady state
$K_{el.ss}$	Terminal elimination rate constant at steady state
$AUC_{(0-\tau),ss}$	AUC over the dosing interval at steady state
$CL/F_{,ss}$	Apparent clearance following oral administration at steady state
$V_z/F_{,ss}$	Apparent volume of distribution during terminal phase at steady state
$C_{avg,ss}$	Average concentration at steady-state
DF%	Peak trough fluctuation
R_{acc}	Accumulation ratio

Pharmacokinetic Parameter Calculation Methods

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin (WNL) Professional (Version **6.3 or higher**) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data. Any subjects with missing concentration data will be included in the PK analysis set provided that at least one PK parameter can be reliably calculated.
- Single dose: All below the limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. Thereafter BLQ values between evaluable concentrations will be substituted by missing before the calculation of the PK variables. Terminal BLQ values will be disregarded.
- Multiple dose: For Day 1, all BLQ values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. For subsequent dosing days not separated by a washout, BLQ values pre-dose, in the absorption phase, and between evaluable concentrations will be substituted by missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.

PK parameters will be estimated according to the following guidelines:

<u>For single dose</u>

- C_{max} will be obtained directly from the concentration-time data.
- t_{max} is the time at which C_{max} is observed.
- K_{el} will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

- A minimum number of three data points in the terminal phase will be used in calculating K_{el} with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}, t_{last}.
- The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.80. Any value less than 0.80 may be used at the PK Scientist's best knowledge and judgment.
- An appropriate number of decimal places should be used for K_{el} to enable the reported value of $t_{½}$ to be calculated.

- $t_{1/2}$ will be calculated as ln2/ K_{el}.
- AUC is calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{(0\text{-}t)} = \int_0^t \mathbf{C(t)dt}$.
  - $AUC_{(0\text{-}inf)} = \int_0^t \mathbf{C(t)dt} + \int_t^\infty \mathbf{C(t)dt} = AUC_{(0\text{-}t)} + C_t/K_{ell.}$
  - C_t is last observed quantifiable concentration.
- $\%AUC_{ex}$ will be calculated as $(1 - [AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}]) \times 100$.
- CL/F will be calculated as dose/$AUC_{(0\text{-}inf)}$, parent drug only.
- V_z/F will be calculated as $CL/F/\lambda_Z$, parent drug only.

For multiple dose

- $C_{max,ss}$ at steady state will be obtained directly from the concentration-time data.
- $C_{min,ss}$ at steady state will be obtained directly from the concentration-time data.
- $t_{max,ss}$ time at which $C_{max,ss}$ occurs at steady state.
- $t_{½,ss}$ will be calculated as ln2/ $K_{el,ss.}$
- $K_{el,ss}$ will be estimated at terminal phase by linear regression
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

- A minimum number of three data points in the terminal phase will be used in calculating $K_{el,ss}$ with the line of regression starting at any post-$C_{max,ss}$ data point ($C_{max,ss}$ should not be part of the regression slope) and including C_{last}, t_{last}.
- The adjusted correlation coefficient (R^2 adj) in general should be greater than 0.80. Any value less than 0.80 may be used at the PK Scientist's best knowledge and judgment.
- An appropriate number of decimal places should be used for $K_{el,ss}$ to enable the reported value of $t_{½,ss}$ to be calculated.

- $AUC_{0-\tau,ss}$ Area under the concentration-time curve over the dosing interval will be calculated using linear trapezoidal method; all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
- $CL/F_{,ss}$ Apparent clearance following oral administration at steady state for the parent drug calculated as dose/ $AUC_{(0-\tau).}$
- $Vz/F_{,ss}$ Apparent volume of distribution during terminal phase at steady state for the parent drug calculated as $CL/F_{,ss} / \lambda_{Z,ss}$.
- $C_{avg,ss}$ Average steady-state concentration calculated as $AUC_{(0\,\tau),ss}/\tau.$

The following PK parameters will also be derived using Statistical Analysis Software (SAS®) (version 9.3 or higher).

- DF% Peak trough fluctuation calculated as 100* ($C_{max,ss}$ - $C_{min,ss}$)/ $C_{avg,ss.}$
- R_{acc} Accumulation ratio calculated as:
  C_{max} (last dose interval)/ C_{max} (first dose interval).
  $AUC_{(0-\tau),ss}$ (last dose interval)/ $AUC_{(0-\tau),ss}$ (first dose interval).

3.2.3 Safety Variables

3.2.3.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs will be coded using the latest available version of MedDRA.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).
- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings.

3.2.3.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured:

- **Hematology:** Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, hemoglobin, hemoglobin, hematocrit, MCV, MCH, MCHC, thrombocytes.
- **Biochemistry:** sodium, potassium, calcium, chloride, inorganic phosphorus, alkaline phosphatase, γ-GT, AST, ALT, total bilirubin, creatinine, glucose, urea BUN, uric acid, total cholesterol, triglycerides, total proteins.
- **Urinalysis:** stick (pH, specific weight, appearance, color, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, hematic pigments, leukocytes), sediment (leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria)
- **Serology:** Hepatitis B (HBs antigen), Hepatitis C (HCV antibodies), HIV 1/2 (HIV Ag/Ab combo).
- **Drugs of abuse:** urine multi-drug kit (cocaine, amphetamine, morphine, cannabis, benzodiazepines, barbital)
- **Pregnancy test:** only for female (serum, urine)

Overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant (NS) or not clinically significant (NCS)) and clinically significant findings (if any) will be reported in the individual eCRFs. All CS abnormalities after the screening visit will be recorded as AEs.

3.2.3.3 Vital Signs

The following vital signs measurements will be obtained:

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Heart rate (bpm)

3.2.3.4 12-Leads ECGs

The ECG recording will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

3.2.3.5 Physical Examination

Full physical examinations will be performed, overall investigator's interpretation (as normal or abnormal and, if abnormal, CS or NCS) and CS abnormalities (if any) will be reported in the individual CRFs.

All CS abnormalities after the screening visit will be recorded as AEs.

3.2.3.6 Prior/Concomitant Medication

Prior and concomitant medication will be coded using the latest version of World Health Organization-Drug Dictionary (WHO-DD) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

'Baseline' is defined as the last available pre-treatment assessment. 'End of Study' is defined as the last available post-treatment assessment. 'Treatment Day' will be calculated relative to the date of randomization i.e. Treatment Day = Assessment Date -Randomization Date + 1. 'Week 1' will be defined as the mean of the Day 1 to Day 7 values, 'Week 2' will be defined as the mean of the Day 8 to Day 14 values and so on.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

4.3 Software Considerations

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

PK analyses will be produced using Phoenix® WinNonLin (WNL) version 6.3 or a later version in a secure and validated environment.

All report outputs will be provided to the Sponsor in RTF format.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

- A summary of the number of subjects screened for entry into the study and the number and percentage of subjects excluded prior to randomization by major reason and overall.
- A summary of the number of subjects randomized, the number and percentage of subjects treated (with at least one dose of study medication) and the number and percentage of subjects withdrawing from study treatment, withdrawing from the study and completing each period of the study by treatment group and overall. Withdrawals from the study and from study treatment should also be summarized by major reason.

By-subject listings of eligibility details, randomization details (including whether the blind was broken at discontinuation), visit dates and withdrawal/study completion details (including reason for discontinuation and duration of treatment prior to discontinuation) should be provided.

4.4.2 Protocol Deviations

All protocol deviations will be recorded by the Investigator and will be listed by subject. All protocol deviations will be discussed between PAREXEL and the Sponsor during the clean file meeting before database lock in order to determine whether these may warrant exclusion of a subject from the statistical analyses.

- A summary of the number and percentage of subjects with a major (decided by sponsor) protocol deviation by treatment group and overall

A by-subject listing of major protocol deviations should be provided.

4.5 Analysis Sets

4.5.1 Randomized Set

The randomized set includes all subjects randomized. This analysis set will be used for demographic, baseline and background characteristics.

4.5.2 Safety Set

The safety set includes all subjects who receive at least 1 dose of IMP. Safety analyses will be based on the treatment actually received, not on the treatment to which the subject was randomized. The safety summaries and analyses will be based on the Safety Set.

4.5.3 Pharmacokinetic Set

The PK Set will include all subjects who have received at least one dose of IMP with at least one primary PK parameter evaluable and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of the compound to be measured. Any data excluded will be discussed at data review meeting before PK parameters are available.

Data may/will be excluded (depending on the protocol and IMP under study) from PK analysis (concentrations listed only) if any of the following criteria are fulfilled:

- Concomitant medication, which could render the plasma concentration time profile unreliable
- The pre-dose concentration is greater than 5% of the corresponding Cmax in any given treatment period.
- Subject vomits within 2 x the reported median t max for the analyte (oral studies only).
- Subject has moderate or severe diarrhea within 2 x the reported median tmax for the analyte (oral studies only).
- Other events which could render the plasma concentration-time profile unreliable (such as AEs, administration errors etc.).

4.6 Demographics and Baseline Characteristics

The summaries and listings provided include the following:

- demographic variables (age, sex, ethnic origin, race, height and weight, Body mass index (BMI)) by treatment group and overall
- other possibly relevant variables (drug, alcohol, and smoking history) by treatment group and overall

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent.

4.7 Medical History and Concomitant Illnesses

All medical history and concomitant illness will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

All medical history and concomitant illness will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each cohort/period and listed using the safety set.

4.8 Prior and Concomitant Medications

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest

that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Prior and concomitant medication will be coded using the latest version of World Health Organization-Drug Dictionary (WHO-DD) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

All prior/concomitant medications will be summarized by ATC4 and Preferred Term (PT) for each cohort/period and listed using the safety set.

4.9 Treatment Exposure / Compliance

Per ICH E3: When the dose in each [subject] can vary, the actual doses received by [subjects] should be shown and individual [subject's] doses should be [presented in a listing].

Study treatment will be administered under the supervision of investigator site personnel. The date and time of IMP administration will be listed by subject using the safety set.

4.10 Pharmacokinetics Evaluation

4.10.1 Pharmacokinetics Concentrations

Pharmacokinetic concentration data for will be listed by subject including actual sampling times relative to cohort/period based on PK set. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as BLQ in the listings. Plasma concentrations will be summarized by dose cohort, period, and nominal timepoint. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(exp(s^2)-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all derived PK concentrations without prior rounding
- The mean, standard deviation (SD), geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- Geometric coefficient of variation (CV) % and coefficient of variation (CV%) will be presented to one decimal place.

Individual plasma concentration versus actual times will be plotted by cohort/period in linear and semi-logarithmic scale. Mean plasma concentrations versus nominal times will also be presented in linear and semi-logarithmic scale.

4.10.1.1 Handling of Values Below the Limit of Quantification (BLQ)

Graphical Presentation

For graphs of arithmetic means all BLQ concentrations will be substituted by zeros. For graphs of geometric means, BLQ concentration values at pre-dose, at all time points up to the first quantifiable concentration, between quantifiable concentrations and after the last quantifiable concentration will be substituted by zero, hence geometric means are not defined and disregarded from displays.

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:

- All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis. Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point.

4.10.1.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® (Version 6.3) or higher. Please refer to section 3.2.2.

Pharmacokinetic parameters will be listed by subject and summarized by cohort and period. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum values. For t_{max}, only median, minimum and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings for PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of t_{max}, which will be presented to two decimal places.
- Parameters derived directly from source data (e.g. C_{max},) shall be reported with the same precision as the source data (if this is not four significant digits).
- The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place.
- For t_{max} the minimum and maximum will be presented to two decimals places and all other descriptive statistics will be presented to three decimal places.

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.11.1 Adverse Events

An AE is any untoward medical occurrence in a study subject administered an IMP which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g. those occurring during treatment-free periods (including Screening or post-treatment Follow-up periods), in association with study-related procedures and assessments.

Concomitant illnesses, which existed before entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as part of the subject's medical history.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Any AEs with incomplete start and end dates/times will be treated as follows:

Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK: NK in the listings (where NK = Not Known).

Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings. Partially complete AE dates will not be imputed in the listings and the available day, month and year components will be used to determine if an adverse event is treatment- emergent taking the first dosing date and end of study date as references.

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be summarized on a per-subject basis and per-event basis. A per-subject basis means that even if a subject reported the same event repeatedly (i.e., events mapped to the same PT) during the trial period, the event will be counted only once. A per-event basis will report the number of events.

- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by SOC, and PT
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by PT
- A summary of the most common treatment-emergent adverse events by PT (reported by > 5% of subjects in any treatment).
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by severity, SOC and PT

- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by causality, SOC and PT

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries.

A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will include: subject identifier, age, sex, race, first dosing date/time, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, causality, seriousness, action taken, and outcome.

4.11.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following listings will be produced:

- Withdrawals/Discontinuation due to AEs (if applicable).
- SAEs (if applicable).
- Death (if applicable).

listings by subject will include: subject identifier, age, sex, race, first dosing date/time, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, causality, seriousness, action taken, and outcome.

4.11.3 Clinical Laboratory Evaluation

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. If visit windows are to be used, the non-missing assessment closest to the mid-point of the visit window will be summarized (including repeat and unscheduled assessments). For across visit summaries (e.g. maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

Overall investigator's interpretation (as normal or abnormal and, if abnormal, CS or NCS and clinically significant findings (if any) will be reported in the individual eCRFs. All CS abnormalities after the screening visit will be recorded as AEs.

Following summaries will be produced:

- A summary of value and changes from baseline for each laboratory parameter by time point
- A summary of the number and percentage of subjects experiencing low, normal or high values at baseline and at post-baseline time points, for selected laboratory parameter (shift table)

A by-subject listing of all laboratory data should be provided, with abnormal values highlighted, and including: subject identifier, age, sex, race, weight and visit. Laboratory reference ranges should also be listed.

Laboratory values (hematology, biochemistry and urinalysis) will be listed by subject and time point including changes from baseline (with the exception of urinalysis).

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess the values outside the clinical reference range and these will be reported as abnormal NCS or abnormal CS.

4.11.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Vital signs data will be listed by subject including changes from baseline. The baseline for the vital signs measurements will be the last pre-dose measurement within each period.

Descriptive statistics will be presented by each cohort/period for both individual values (N, mean, SD, median, minimum, maximum) and changes from baseline.

12-Leads ECG

All ECG parameters obtained from the ECG measurement will be listed by subject for study time point including changes from baseline. The baseline for the ECG measurements the last pre-dose measurement within each period.

Descriptive statistics (for non-categorical data) will be presented by each cohort/period for both individual values (N, mean, SD, median, minimum, maximum) and changes from baseline.

Qualitative data will be summarized using frequency counts in each category for each scheduled time point.

Physical Examination

The results of the physical examination will be listed by subject and study time point.

4.12 Determination of Sample Size

12 healthy male and female Chinese subjects / cohort (24 in total) will be included in the study in order to have at least 8 completers / cohort. Drop-out subjects will not be replaced.

Since no hypothesis will be tested, no formal sample size calculation has been performed. The sample size of this study has been determined in agreement with the guidance issued by the Chinese Food and Drug Administration (CFDA) for clinical pharmacokinetic studies.

4.13 Changes in the Conduct of the Study or Planned Analysis

NA

5 REFERENCES

[1] CFDA Guidance
[2] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
[3] Phoenix®WinNonlin® Professional Software Version 6.3 https://www.certara.com

6 APPENDICES

STUDY SCHEDULE

ACTIVITIES		Period 1					
	Screening	Single Dose					
Visit	V1	V2	V3			V4	
Day	Day -14/-2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5
Informed consent	x						
Demography	x						
Lifestyle	x						
Medical and surgical history	x						
Physical examination[3]	x						
Prior and concomitant medications	x	x	x	x	x	x	x
Height	x						
Body Weight[3]	x						
Laboratory analysis[4]	x						
Virology	x						
Serum pregnancy test (women)	x						
Urine multi-drug kit test	x	x					
Blood pressure and heart rate[5]	x		x	x	x		
Alcohol breath test		x					
Urine pregnancy test (women)		x					
ECG[6]	x						
Inclusion/exclusion criteria	x	x					
Subject eligibility	x	x					
Enrolment and randomisation		x					
Confinement		x	x	x			
Discharge					x		
Ambulatory visits						x	
Investigational product administration			x[7]				
Blood sampling for PK analysis			x[8]	x[8]	x[8]	x[8]	x[8]
Standardised meals[11]		x	x	x	x		
Adverse event monitoring[12]	x	x	x	x	x	x	x

ACTIVITIES	Period 2											Final visit/ETV[1]
	Multiple Dose											
Visit	V5		V6				V7				V8	
Day	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 18[2]
Informed consent												
Demography												
Lifestyle												
Medical and surgical history												
Physical examination[3]												x
Prior and concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Height												
Body Weight[3]												x
Laboratory analysis[4]												x
Virology												
Serum pregnancy test (women)												
Urine multi-drug kit test												
Blood pressure and heart rate[5]	x	x	x	x	x	x	x	x	x	x	x	x
Alcohol breath test												
Urine pregnancy test (women)												
ECG[6]												x
Inclusion/exclusion criteria												
Subject eligibility												
Enrolment and randomisation												
Confinement	x	x					x	x	x	x		
Discharge		x								x		
Ambulatory visits			x	x	x	x					x	
Investigational product administration	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]	x[7]					
Blood sampling for PK analysis	x[9]	x[9]	x[10]	x[10]	x[10]	x[10]	x[8]	x[8]	x[8]	x[8]	x[8]	
Standardised meals[11]	x	x					x	x	x			
Adverse event monitoring[12]	x	x	x	x	x	x	x	x	x	x	x	x

1. *Early termination visit (ETV)*
2. *Final visit on day 18*
3. *Physical examination, including body weight, at screening and final visit/ETV*
4. *Laboratory analyses at screening and final visit/ETV*
5. *At pre-dose, at 2 h and 96 h after day 1 single dose and day 14 last multiple dose. At pre-dose, 2 h and 24 h after the day 8 first multiple dose. Before blood sampling and investigational product administration during ambulatory visits*
6. *At screening and final visit/ETV*
7. *On day 1 (Period 1) and once daily from day 8 to day 14 (Period 2), at 8:00 ± 1 h*
8. *At pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 36, 48, 72 and 96 h post-dose after the first single dose (day 1) and the last multiple dose (day 14);*
9. *At pre-dose (0) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (day 8)*
10. *At pre-dose (0) on each day (day 10-13)*
11. *Day -1: standardised dinner;*

Day 1, Day 8, Day 14: standardised lunch at approximately 5 h post-dose, standardised dinner at approximately 13 h post-dose;

Day 2, Day 9 and Days 15/16: standardised breakfast, lunch and dinner

12. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*

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PAREXEL International

Zambon SpA

Z7219J03

A PHASE I, PHARMACOKINETICS, SAFETY AND TOLERABILITY STUDY OF SINGLE AND MULTIPLE ORAL DOSES OF SAFINAMIDE IN HEALTHY ADULT CHINESE VOLUNTEERS

Statistical Analysis Plan

Version: 2.0

PAREXEL Project Number: CCI

SPONSOR SIGNATURE PAGE

Approved by:

PPD PPD Zambon SpA	Date

PAREXEL International

Sponsor / 3rd Party Vendor Sign-Off

Title: Z7219J03 (CCI) SAP version 2.0 20191014 Sign-Off			
Sponsor Project Number:	Z7219J03	**PAREXEL Project Number:**	CCI
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Signatures below confirm that the Statistical Analysis Plan was developed in accordance with CCI and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: PPD PPD Project Role: PPD

	Signatory
Reviewer	PPD Project Role: PPD PPD Project Role: PPD PPD Project Role: PPD PPD Project Role: PPD

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	12 Dec 2018	New Document
1.1	NA	Updates per finalized protocol amendment and finalized eCRF. (The first version was based on draft protocol and not based on eCRF so that the analyses described were not comprehensive)
1.2	NA	Address internal review comments
1.3	NA	Address sponsor review comments
1.4	NA	Updates per draft shells after sponsor review; Simplified the definition for prior and concomitant medications.
1.5	NA	Address internal review comments
1.6	NA	Address sponsor comments: added one period (pre-treatment). And minor updates from shells comments.
2.0	10 Oct 2019	Please refer to changes in 1.1-1.6

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	AUC from time zero extrapolated to infinity
$AUC_{(0\text{-}t)}$	AUC from time zero to the last quantifiable concentration
$AUC_{(0\text{-}24h)}$	AUC from time zero to 24h after administration
$AUC_{(0\text{-}24h),ss}$	AUC from time zero to 24h after administration at steady state
AUC%extrap	Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
$C_{ave,ss}$	Average concentration at steady state
CFDA	Chinese Food and Drug Administration
CI	Confidence interval
C_{last}	Last quantifiable concentration at t_{last}
CL_R	Renal clearance
CL/F	Apparent clearance following oral administration
$CL/F_{,ss}$	Apparent clearance following oral administration at steady state
CRF	Case Report Form
CSP	Clinical Study Protocol
C_{max}	Maximum observed concentration
$C_{max,ss}$	Maximum observed concentration at steady state
C_{min}	Minimum observed concentration in the dosing interval
$C_{min,ss}$	Minimum observed concentration at steady state
CS	Clinically significant

Abbreviation / Acronym	Definition / Expansion
CV	Coefficient of variation
DBP	Diastolic blood pressure
DF%	Peak-trough fluctuation over one dosing interval at steady-state
DRM	Data Review Meeting
ECG	Electrocardiogram
ETV	Early termination visit
γ-GT	γ-Glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IMP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
$MRT_{(0\text{-}inf)}$	Mean residence time extrapolated to infinity
$MRT_{(0\text{-}inf),ss}$	Mean residence time at steady state extrapolated to infinity
NA	Not available
NCS	Not clinically significant
NK	Not known
OTC	Over the counter
PK	Pharmacokinetic
R_{acc}	Accumulation ratio
RBC	Red Blood Cells
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation / Acronym	Definition / Expansion
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error of the mean
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
$t_{½,ss}$	Apparent terminal elimination half-life at steady state
t_{last}	Time of last quantifiable concentration
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to occurrence of C_{max}
$t_{max,ss}$	Time corresponding to occurrence of $C_{max,ss}$ at steady state
V_d/F	Apparent volume of distribution during terminal phase
$V_d/F_{,ss}$	Apparent volume of distribution during terminal phase at steady state
WHODrug Global	World Health Organization Drug Global
K_{el}	Terminal elimination rate constant
$K_{el\ ,ss}$	Terminal elimination rate constant at steady state
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation

1 INTRODUCTION

The present study will be part of safinamide registration package in China and was designed according to Chinese Food and Drug Administration (CFDA) guideline recommendations [1]. Safinamide has been granted marketing authorization in EU (2015), US (2017) and Switzerland (2015).

The α-aminoamide derivative safinamide [(S)-(+)-2-[4-(3-fluorobenzyloxy) benzylamino] propanamide], developed as methane sulfonate salt, is an original anticonvulsant and antiparkinson agent which has been granted marketing authorization in 9 EU Member States (i.e. Germany, Italy, Spain, Portugal, United Kingdom, Belgium, The Netherlands, Sweden and Denmark), in Norway and in Switzerland under the brand name of Xadago®, 50 and 100 mg, film-coated tablets [2], for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal product in mid-to late-stage fluctuating patients [3].

In the present study, safinamide pharmacokinetic profile, safety and tolerability after single dose and at steady state will be investigated for the first time in Chinese healthy male and female volunteers.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 2.0 (April 18, 2019)
- electronic Case Report Form (eCRF), Version 1.0 (May 7, 2019)

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Post database lock modifications will be documented as Statistical Analysis Modification Requests.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate plasma safinamide pharmacokinetic parameters after single and multiple dose administration of the investigational products.

2.2 Secondary Objective

- To collect safety and tolerability data after single and multiple dose administration of the investigational products.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase I, single center, single and multiple-dose, open-label, randomized, parallel-group, pharmacokinetics, safety and tolerability study.

The study population will consist of 24 adult healthy male and female subjects (12 per cohort). Subjects will be randomized to two study cohorts to receive single and multiple doses of 50 mg safinamide (cohort 1), or single and multiple doses of 100 mg safinamide (cohort 2), according to the study randomized, parallel-group design, as follows:

Cohort	Period 1 - single dose Day 1	Washout	Period 2 - Multiple doses Days 8 - 14
Cohort 1	50 mg po	7 days	50 mg po o.d for 7 days
Cohort 2	100 mg po		100 mg po o.d. for 7 days

3.2 Endpoints and Associated Variables

3.2.1 Efficacy Variables

Not applicable.

3.2.2 Pharmacokinetic Variables

Unless otherwise stated, derivation of Pharmacokinetic (PK) parameters will be the responsibility of Qualitative Clinical Development (QCD), PAREXEL International. The following PK parameters will be determined for Investigational Medicinal Product (IMP) in plasma following single dose and multiple dose administration:

Table 1 Pharmacokinetic Parameters after Single Dose Administration

Parameter	Definition
C_{max} [1]	Maximum observed concentration
t_{max} [1]	Time corresponding to occurrence of C_{max}
$t_{½}$	Apparent terminal elimination half life
Clast/Ct	Last quantifiable concentration
AUMC	Area under the first moment of the concentration-time curve
K_{el}	Terminal elimination rate constant
$AUC_{(0-t)}$ [1]	AUC from time zero to the last quantifiable concentration
$AUC_{(0-24)}$ [1]	AUC over the dosing interval (24 hours)
$AUC_{(0-inf)}$	AUC from time zero extrapolated to infinity
$\%AUC_{ex}$	Percentage of $AUC_{(0-inf)}$ obtained by extrapolation
MRT	AUMC/AUC
CL/F	Apparent clearance following oral administration
V_d/F	Apparent volume of distribution during terminal phase

[1] These parameters will also be calculated after first multiple dose (day 8).

Table 2 Pharmacokinetic Parameters after Multiple Dose Administration

Parameter	Definition
$C_{max,ss}$	Maximum observed concentration at steady state
$C_{min,ss}$	Minimum observed concentration at steady state
$t_{max,ss}$	Time corresponding to occurrence of $C_{max,ss}$ at steady state
$K_{el.ss}$	Terminal elimination rate constant at steady state
$AUC_{(0-t),ss}$	AUC to last observed concentration at steady state
$AUC_{(0-\tau),ss}$	AUC over the dosing interval at steady state
$CL/F_{,ss}$	Apparent clearance following oral administration at steady state
$V_d/F_{,ss}$	Apparent volume of distribution during terminal phase at steady state
$C_{ave,ss}$	Average concentration at steady-state
DF%	Peak trough fluctuation
$R_{acc,AUC}$	Accumulation ratio, based on AUC
$R_{acc,Cmax}$	Accumulation ratio, based on C_{max}

Pharmacokinetic Parameter Calculation Methods

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin (WNL) Professional (Version **8.0**) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data. Any subjects with missing concentration data will be included in the PK analysis set provided that at least one PK parameter can be reliably calculated.
- Single dose: All below the limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. Thereafter BLQ values between evaluable concentrations will be substituted by missing before the calculation of the PK variables. Terminal BLQ values will be disregarded.

- Multiple dose: For Day 1, all BLQ values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. For subsequent dosing days not separated by a washout, BLQ values pre-dose, in the absorption phase, and between evaluable concentrations will be substituted by missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.

PK parameters will be estimated according to the following guidelines:

For single dose

- C_{max} will be obtained directly from the concentration-time data.
- t_{max} is the time at which C_{max} is observed.
- K_{el} will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
  - A minimum number of three data points in the terminal phase will be used in calculating K_{el} with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}, t_{last}.
  - The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.80. Any value less than 0.80 may be used at the PK Scientist's best knowledge and judgment.
  - An appropriate number of decimal places should be used for K_{el} to enable the reported value of $t_{½}$ to be calculated.
- $t_{1/2}$ will be calculated as ln2/ K_{el}.
- AUC is calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{(0\text{-}t)} = \int_0^t \mathbb{C}(t)\mathbf{dt}$.
  - $AUC_{(0\text{-}inf)} = \int_0^t \mathbb{C}(t)\mathbf{dt} + \int_t^\infty \mathbb{C}(t)\mathbf{dt} = AUC_{(0\text{-}t)} + C_t/K_{el}$.
  - C_t is last observed quantifiable concentration.
- $\%AUC_{ex}$ will be calculated as $(1 - [AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}]) \times 100$.

- CL/F will be calculated as dose/$AUC_{(0\text{-}inf)}$, parent drug only.
- V_d/F will be calculated as (CL/F)/Kel, parent drug only.

For multiple dose

- $C_{max,ss}$ at steady state will be obtained directly from the concentration-time data.
- $C_{min,ss}$ at steady state will be obtained directly from the concentration-time data.
- $t_{max,ss}$ time at which $C_{max,ss}$ occurs at steady state.
- $K_{el,ss}$ will be estimated at terminal phase by linear regression
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
  - A minimum number of three data points in the terminal phase will be used in calculating $K_{el,ss}$ with the line of regression starting at any post-$C_{max,ss}$ data point ($C_{max,ss}$ should not be part of the regression slope) and including C_{last}, t_{last}.
  - The adjusted correlation coefficient (R^2 adj) in general should be greater than 0.80. Any value less than 0.80 may be used at the PK Scientist's best knowledge and judgment.
  - An appropriate number of decimal places should be used for $K_{el,ss}$ to enable the reported value of $t_{½,ss}$ to be calculated$AUC_{0\text{-}24,ss}$
- Area under the concentration-time curve over the dosing interval will be calculated using linear trapezoidal method; all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
- CL /$F_{,ss}$ Apparent clearance following oral administration at steady state for the parent drug calculated as dose/ $AUC_{(0\text{-}24,ss).}$
- V_d /$F_{,ss}$ Apparent volume of distribution during terminal phase at steady state for the parent drug calculated as ($CL/F_{,ss}$)/ Kel_{ss}.
- $C_{avg,ss}$ Average steady-state concentration calculated as $AUC_{(0\ \tau),ss}/\tau$.

The following PK parameters will also be derived using Statistical Analysis Software (SAS®) (version 9.3 or higher).

- DF% Peak trough fluctuation calculated as 100* ($C_{max,ss}$ - $C_{min,ss}$)/ $C_{avg,ss}$.
- $R_{acc,AUC}$ and $R_{acc,Cmax}$ Accumulation ratio calculated as:
  C_{max} (last dose interval)/ C_{max} (first dose interval).
  $AUC_{(0-\tau),ss}$ (last dose interval)/ $AUC_{(0-24)}$ (first dose interval).

3.2.3 Safety Variables

3.2.3.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a study subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the medicinal product. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g. those occurring during treatment-free periods (including Screening or post-treatment Follow-up periods), in association with study-related procedures and assessments.

Concomitant illnesses, which existed before entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as part of the subject's medical history.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs) according to the period of occurrence. A PTAE is defined as an AE occurring before the first dose of investigational product and not worsening after the first dose of investigational product. A TEAE is defined as an AE that occurring or worsening after the first dose of investigational product. Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started or worsen in severity prior to the first dose of study treatment.

Any AEs with incomplete start and end dates/times will be treated as follows:

Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings (where NK = Not Known). Partially complete AE dates will not be imputed in the listings and the available day, month and year components will be used to determine if an adverse event is treatment-emergent taking the first dosing date and end of study date as references.

The severity of an AE will be evaluated by the investigator and recorded in the eCRF as Mild, Moderate, or Severe. The investigator will also perform an evaluation with respect to seriousness and causality (relationship of any AE to IMP, whether believed by the investigator to be related or unrelated to the IMP) of the AEs and record it on the appropriate section of the eCRF.

3.2.3.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured:

- **Hematology:** Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, thrombocytes.
- **Biochemistry:** sodium, potassium, calcium, chloride, inorganic phosphorus, alkaline phosphatase, γ-GT, AST, ALT, total bilirubin, creatinine, glucose, urea or BUN, uric acid, total cholesterol, triglycerides, total proteins.
- **Urinalysis:** pH, specific gravity, appearance, color, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, leukocytes, erythrocytes, epithelial cells, crystals, cylinders.

Overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant [NS] or not clinically significant [NCS]) and clinically significant findings (if any) will be reported in the individual eCRFs. All CS abnormalities after the screening visit will be recorded as AEs.

3.2.3.3 Vital Signs

The following vital signs measurements will be obtained:

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Heart rate (beats/min)

3.2.3.4 Body Weight

3.2.3.5 12-Leads Electrocardiograms (ECGs)

The ECG recording will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

All CS abnormalities after the screening visit will be recorded as AEs.

3.2.3.6 Physical Examination

Full physical examinations will be performed, overall investigator's interpretation (as normal or abnormal and, if abnormal, CS or NCS) and CS abnormalities (if any) will be reported in the individual eCRFs.

All CS abnormalities after the screening visit will be recorded as AEs.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

Each cohort has three periods (pre-treatment period, single dose period (Day 1) and multiple doses period (Day 8 to Day 18)) with a washout duration of 7 days between single dose period and multiple dose period. Period will be displayed for subject listings where applicable. 'Baseline' is defined as the last available assessment prior to the first dose of study treatment (per period when pre-dose assessment is available for both of the single dose and multiple dose periods). 'End of Study' is defined as the last available post-treatment assessment. 'Study Day' will be calculated relative to the first dose date of study treatment i.e. Study Day = Assessment Date -First Dose Date + 1 (+ 1 if assessment date is on or after the first dose date).

Continuous data will be summarized in terms of the mean, standard deviation (SD), coefficient of variation (CV) (%), median, minimum, maximum and number of observations, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. The CV(%) will be presented to one decimal place. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using the number of subjects included in the corresponding set of subjects that is indicated in the title of the tables as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

4.3 Software Considerations

All report outputs will be produced using SAS® version 9.3 or a later version [4] in a secure and validated environment.

The PK parameters will be produced using Phoenix® WinNonLin (WNL) version 8.0 [5] in a secure and validated environment.

All report outputs will be provided to the Sponsor in RTF and/or PDF format.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A subject will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures. A subject will be defined as eligible if he/she meets all the inclusion criteria and not meet any exclusion criteria. Otherwise he/she will be defined as a

screen failure. A subject will be defined as enrolled in the study if he/she is included into the interventional phase of the study. The enrollment will be performed through randomized allocation to a treatment cohort. An eligible but not enrolled subject will be defined as a reserve. A subject will be defined as randomized in the study when he/she is assigned to a randomized treatment cohort. A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

- A summary of the number of subjects screened for entry into the study and the number and percentage of eligible subjects, screen failure subjects (including the reason for screen failure), enrolled subjects, and randomized subjects.
- A summary of the number of subjects randomized, the number and percentage of subjects treated (with at least one dose of study medication) and the number and percentage of subjects withdrawing from study treatment and withdrawing from the study by treatment cohort and overall. Withdrawals from the study and from study treatment should also be summarized by major reason. Primary reason of study discontinuation or study treatment discontinuation will be documented as one of the following:
  - Adverse event
  - Death
  - Lost to follow-up
  - Non-compliance with study drug
  - Physician decision
  - Pregnancy
  - Protocol deviation
  - Study terminated by sponsor
  - Technical problem
  - Withdrawal by subject
  - Other

By-subject listings of eligibility details, randomization details and study treatment/study discontinuation/completion details (including reason for discontinuation) will be provided.

4.4.2 Protocol Deviations

All protocol deviations will be recorded by the Investigator. Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. The impact of major protocol deviations will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification and approved by Sponsor. All major protocol deviations will be discussed between PAREXEL and the Sponsor during the data review meeting shortly before database lock in order to determine whether these may warrant exclusion of a subject from the statistical analyses. Results and population assignments will be summarized in a meeting minute/report and will be signed off by all relevant scientific experts.

- A summary of the number and percentage of subjects with a major (approved by sponsor) protocol deviation by treatment cohort and overall

A by-subject listing of major protocol deviations should be provided.

4.5 Analysis Sets

The number and percentage of subjects within each analysis set will be summarized based on all enrolled subjects. A by-subject listing, including the reasons of being excluded from a specific analysis set, will also be provided.

4.5.1 Randomized Set

The randomized set includes all subjects randomized. This analysis set will be used for the analysis of demographic, baseline and background characteristics. If a subject is allocated to the incorrect treatment cohort as per the study randomization list, the subject will be summarized and analyzed 'as randomized' i.e. by randomized treatment cohort.

4.5.2 Safety Set

The safety set includes all randomized subjects who receive at least one dose of IMP. Safety analyses will be based on the treatment cohort actually received, not on the treatment cohort to

which the subject was randomized. The safety summaries and analyses will be based on the Safety Set.

4.5.3 Pharmacokinetic Set

The PK Set will include all randomized subjects who fulfil the study protocol requirements in terms of IMP intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. Any data excluded will be discussed at data review meeting before database lock. PK analyses will be based on the treatment cohort actually received, not on the treatment cohort to which the subject was randomized. The PK summaries and analyses will be based on the PK set.

Subjects may/will be excluded (depending on the protocol and IMP under study) from PK set if any of the following criteria are fulfilled:

Before statistical analysis

- Vomiting and diarrhea after drug intake which could render the plasma concentration-time profile unreliable.
- Intake of concomitant medications which could render the plasma concentration-time profile unreliable.
- AEs which could render the plasma concentration-time profile unreliable.
- Administration errors which could render the plasma concentration-time profile unreliable.
- Other events which could render the plasma concentration-time profile unreliable.

After bioanalysis

Subjects can be excluded from PK set only for the reason below:

- Subject with non-zero baseline concentrations > 5% of C_{max} for single dose and first multiple dose (day 1 and day 8).

The samples from the subjects excluded from the PK set should still be assayed and the results listed. Subjects should not be excluded from the PK set if the AUC_{0-t} covers less than 80% of the $AUC_{0-\infty}$.

4.6 Demographics and Baseline Characteristics

The summaries and listings that will be provided include the following:

- demographic variables (age, sex, ethnicity, height, weight, and body mass index [BMI]) by treatment cohort and overall
- other possibly relevant variables (drug, alcohol, caffeine, and smoking history) by treatment cohort and overall
- other baseline characteristics (virology, pregnancy test, urine drug test, alcohol breath test)

4.7 Medical and Surgical History

All medical and surgical history will be coded using the MedDRA version 22.0.

All medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment cohort and listed by subject using the safety set.

4.8 Prior and Concomitant Medications

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior, or Concomitant.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior. If a medication stops on or after the date of first dose of study medication, then the medication will be classified as Concomitant.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior.

Prior and concomitant medication will be coded using the WHODrug Global Version Mar 2019 or later and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

All prior/concomitant medications will be summarized by ATC level 3 term and PT for each treatment cohort and listed by subject using the safety set.

Information of concomitant procedures, including any surgical, therapeutic or diagnostic procedures, will only be collected for adverse events and serious adverse events, and will be coded using the MedDRA version 22.0. All concomitant procedures will be summarized by SOC and PT for each cohort and listed by subject based on the safety set.

4.9 Treatment Exposure / Compliance

Study treatment will be administered under the supervision of investigator site personnel. The date and time of IMP administration will be listed by subject using the safety set.

4.10 Pharmacokinetics Evaluation

4.10.1 Pharmacokinetics Concentrations

Pharmacokinetic concentration data for will be listed by subject including nominal sampling times relative to cohort/period/day based on PK set. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as BLQ in the listings. Plasma concentrations will be summarized by dose cohort, period, day and nominal timepoint. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(exp(s^2)-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all PK concentrations without prior rounding
- The mean, standard deviation (SD), geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- Geometric coefficient of variation (gCV) % and coefficient of variation (CV%) will be presented to one decimal place.

Individual plasma concentration versus actual times will be plotted by cohort/period/day in linear and semi-logarithmic scale. Mean plasma concentrations (±SD) versus nominal times will also be presented in linear and semi-logarithmic scale.

4.10.1.1 Handling of Values Below the Limit of Quantification (BLQ)

Graphical Presentation

For graphs of arithmetic means all BLQ concentrations will be substituted by zeros. For graphs of geometric means, BLQ concentration values at pre-dose, at all timepoints up to the first quantifiable concentration, between quantifiable concentrations and after the last quantifiable concentration will be substituted by zero, hence geometric means are not defined and disregarded from displays.

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:

- All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis. Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point.

4.10.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® (Version 8.0). Please refer to section 3.2.2.

Pharmacokinetic parameters will be listed by subject and summarized by cohort, period, and day. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum values. For t_{max}, only median, minimum and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings for PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of t_{max}, which will be presented to two decimal places.

- Parameters derived directly from source data (e.g. C_{max},) shall be reported with the same precision as the source data (if this is not four significant digits).
- The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place.
- For t_{max} the minimum and maximum will be presented to two decimals places and all other descriptive statistics will be presented to three decimal places.

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.11.1 Adverse Events

All AE data will be listed individually by subject. Only TEAEs will be included in the summary tables. Any PTAEs will be included in the data listings but will not be included in the summary tables of AEs.

AEs will be summarized on per-subject basis and per-event basis. A per-subject basis means that even if a subject reported the same event repeatedly (i.e., events mapped to the same PT) during the trial period, the event will be counted only once. A per-event basis will report the number of events.

An overview table will be summarized for the following categories:

- Any TEAEs
- Any TEAEs related to study drug
- Any severe TEAEs
- Any severe TEAEs related to study drug
- Any TEAEs leading to drug interruption
- Any TEAEs leading to drug withdrawal
- Any TEAEs with outcome of death
- Any TEAEs with outcome of death, related to study drug
- Any SAEs (including events with outcome of death)

- Any SAEs (including events with outcome of death), related to study drug
- Any SAEs leading to drug withdrawal

The following summaries will be produced:

- A summary of TEAEs by SOC, and PT
- A summary of TEAEs by PT
- A summary of the most common TEAEs by PT (reported by > 5% of subjects in any treatment cohort).
- A summary of TEAEs by seriousness, SOC and PT
- A summary of TEAEs by severity, SOC and PT
- A summary of TEAEs by causality, SOC and PT

AE summaries will be displayed by period (single dose and multiple dose) and ordered in terms of decreasing frequency in total column for SOC and PT within SOC, and then alphabetically by SOC and PT within SOC. For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summary. Similarly, the worst seriousness will be attributed and used in the by seriousness summary, the worst causality (most related to treatment) will be attributed and used in the by-causality summary. If severity, seriousness or causality is missing, no imputation will be applied.

A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will include: subject identifier, age, sex, ethnicity, treatment cohort, period, adverse event (SOC, PT, and verbatim term), start date, end date, severity, causality, seriousness, action taken, and outcome.

4.11.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Other significant adverse events are those adverse events reported as leading to drug interruption, drug withdrawal, or study discontinuation.

The following by-subject listings will be produced (if applicable):

- A listing of AEs leading to drug interruption
- A listing of AEs leading to drug withdrawal

- A listing of AEs leading to study discontinuation
- A listing of SAEs
- A listing of all deaths

Listings should follow the format described for AEs in Section 4.11.1 if appropriate.

4.11.3 Clinical Laboratory Evaluation

Summaries will be presented for the overall interpretation of the laboratory data. The number and percentages of subjects within each if the interpretation categories (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) will be summarized in these tables.

By-subject listings of all laboratory data will be provided including: subject identifier, age, sex, ethnicity, weight and visit. Laboratory reference ranges should also be listed. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

4.11.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Vital signs data will be listed by subject. Descriptive statistics of individual values will be presented by treatment cohort at scheduled visit/time point.

Body Weight

Body weight values will be summarized descriptively by treatment cohort at schedule visit. Corresponding data will be listed by subject.

12-Leads ECG

The overall investigator's interpretation for ECG will be listed by subject and study time point.

Physical Examination

The results of the physical examination will be listed by subject and study time point.

4.12 Determination of Sample Size

Twelve healthy male and female Chinese subjects / cohort (24 in total) will be included in the study in order to have at least 8 completers / cohort. Drop-out subjects will not be replaced.

Since no hypothesis will be tested, no formal sample size calculation has been performed. The sample size of this study has been determined in agreement with the guidance issued by the CFDA for clinical pharmacokinetic studies.

4.13 Changes in the Conduct of the Study or Planned Analysis

NA

5 REFERENCES

[1] CFDA Guidance
[2] EMA Commission Implementing Decision C (2015) 1390 (final) – Xadago (safinamide). 24 February 2015
[3] Summary of Product Characteristics (SmPC) – Xadago 50 mg, 100 mg film-coated tablets
[4] SAS® Version 9.3 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
[5] Phoenix®WinNonlin® Professional Software Version 8.0 https://www.certara.com

6 APPENDICES

STUDY SCHEDULE

ACTIVITIES		Period 1		
	Screening	Single Dose		
Visit	V1	V2	V3	V4
Day	Day -14/-2	Day -1	Day 1/3	Day 4/5
Informed consent	x			
Demography	x			
Lifestyle	x			
Medical and surgical history	x			
Physical examination[3]	x			
Prior and concomitant medications	x	x	x	x
Height	x			
Body Weight[3]	x			
Laboratory analysis[4]	x			
Virology	x			
Serum pregnancy test (women)	x			
Urine multi-drug kit test	x	x		
Blood pressure and heart rate[5]	x		x (Day 1: pre-dose, 2 hours post-dose)	x (Day 5: 96 hours after Day 1)
Alcohol breath test		x		
Urine pregnancy test (women)		x		
ECG[6]	x			
Inclusion/exclusion criteria	x	x		
Subject eligibility	x	x		
Enrolment and randomisation		x		
Confinement		x	x	
Discharge			x (Day 3)	
Ambulatory visits				x
Investigational product administration			x[7] (Day 1)	
Blood sampling for PK analysis			x[8]	x[8]
Standardized meals[11]		x	x	
Adverse event monitoring[12]	x	x	x	x

ACTIVITIES	Period 2				Final visit/ETV[1]
	Multiple Dose				
Visit	V5	V6	V7	V8	
Day	Day 8/9	Day 10/13	Day 14/17	Day 18	Day 18[2]
Informed consent					
Demography					
Lifestyle					
Medical and surgical history					
Physical examination[3]					x
Prior and concomitant medications	x	x	x	x	x
Height					
Body Weight[3]					x
Laboratory analysis[4]					x
Virology					
Serum pregnancy test (women)					
Urine multi-drug kit test					
Blood pressure and heart rate[5]	x (Day 8: pre-dose, 2 hours post-dose)	x	x (Day 14: pre-dose, 2 hours post-dose)	x (Day 18: 96 hours after Day 14)	x
Alcohol breath test					
Urine pregnancy test (women)					x
ECG[6]					x
Inclusion/exclusion criteria					
Subject eligibility					
Enrolment and randomisation					
Confinement	x		x		
Discharge	x (Day 9)		x (Day 17)		
Ambulatory visits		x		x	
Investigational product administration	x[7]	x[7]	x[7] (Day 14)		
Blood sampling for PK analysis	x[9]	x[10]	x[8]	x[8]	
Standardized meals[11]	x		x		
Adverse event monitoring[12]	x	x	x	x	x

1. *Early termination visit (ETV)*
2. *Final visit on day 18*
3. *Physical examination, including body weight, at screening and final visit/ETV*
4. *Laboratory analyses at screening and final visit/ETV*
5. *At pre-dose, at 2 h and 96 h after day 1 single dose and day 14 last multiple dose. At pre-dose and 2 h after the day 8 first multiple dose. Before blood sampling and investigational product administration during ambulatory visits*
6. *At screening and final visit/ETV*
7. *On day 1 (Period 1) and once daily from day 8 to day 14 (Period 2), at 8:00 ± 1 h*
8. *At pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 36, 48, 72 and 96 h post-dose after the first single dose (day 1) and the last multiple dose (day 14);*
9. *At pre-dose (0) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (day 8)*
10. *At pre-dose (0) on each day (day 10-13)*
11. *Day -1: standardised dinner;*

    Day 1, Day 8, Day 14: standardized lunch at approximately 5 h post-dose, standardized dinner at approximately 13 h post-dose;

    Day 2 and Days 15/16: standardized breakfast, lunch and dinner

    Day 3, Day 9 and Day 17: standardized breakfast
12. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*

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