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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CLINICAL TRIAL PROTOCOL

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

Phase I, single centre, single and multiple-dose, open-label, randomised, parallel-group, pharmacokinetics, safety and tolerability study

Protocol Code: Z7219J03

Date: 10-December-2018

Version: Final 1.0

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APPROVAL PAGE

Clinical Trial Title:	A phase I, pharmacokinetics, safety and tolerability study of single and multiple oral doses of safinamide in Chinese adult healthy volunteers.
Protocol Code	Z7219J03
Date:	10-December-2018
Author:	PPD
Sponsor Name and Address:	Zambon SpA Via Lillo del Duca 10 20091 Bresso, Milan, Italy

As agreed and approved:

_____/_____/_____	_____	_____
Date (dd/Mmm/yyyy)	**Principal Investigator**	**SIGNATURE**

Accepted for the Sponsor

_____/_____/_____	_____	_____
Date (dd/Mmm/yyyy)	**Global Chief Medical Officer and Patient's Access Head**	**SIGNATURE**

1 STUDY SYNOPSIS

Title: A phase I, pharmacokinetics, safety and tolerability study of single and multiple oral doses of safinamide in healthy adult Chinese volunteers

Protocol number: Z7219J03

Clinical phase: Phase I

Study design: Phase I, single centre, single and multiple-dose, open-label, randomised, parallel-group, pharmacokinetics, safety and tolerability study

Planned nr. of centres / countries: 1/China

Investigator and centre: *Principal investigator*: TBD

Investigational products:
Test product 1: Xadago® 50 mg safinamide film-coated tablets, Zambon S.p.A., Italy
Test product 2: Xadago® 100 mg safinamide film-coated tablets, Zambon S.p.A., Italy

Dose regimen:
Subjects will be randomised 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) as follows:
Cohort 1: One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets administered o.d. from day 8 to day 14.
Cohort 2: One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7safinamide 100 mg film-coated tablets administered o.d. from day 8 to day 14.

Study treatment is also summarised in the scheme below:

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

The investigational products will be orally administered in the morning, at 8:00±1h, under fasting conditions, with 240 mL (total volume) of still mineral water. A mouth-and-hand check will be performed immediately after dosing to ensure treatment compliance.

Objective: To evaluate safinamide pharmacokinetic profile, safety and tolerability after single and multiple dose administration to healthy adult Chinese volunteers.

End-points:
Primary end-point:
- To evaluate plasma safinamide pharmacokinetic parameters after single and multiple dose administration of the Test investigational products.

Secondary end-points:
- To collect safety and tolerability data after single and multiple dose administration of the Test investigational products.

Study variables:
Primary variables - Pharmacokinetics: The following safinamide PK parameters will be determined on day 1 (after the first dose), on day 8 (after the first multiple dose) and on day 14 (after the last dose):

After single dose and first multiple dose (day 1 and day 8):
- C_{max}: maximum safinamide plasma concentration
- t_{max}: time to achieve C_{max}
- AUC_{0-t}: area under the concentration-time curve from single dose administration to the last observed concentration time t, calculated with the linear up/log down trapezoidal method
- AUC_{0-24}: area under the concentration-time curve in the tau interval (from single dose administration to 24 h post-dose), calculated with the linear up/log down trapezoidal method

STUDY SYNOPSIS (cont.)

Study variables, continued: **Primary variables - Pharmacokinetics, continued:**

After single dose only (day 1):

- Kel: terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points
- $t_{1/2}$: apparent terminal elimination half-life, calculated, if feasible, as $\ln 2/K_{el}$
- $AUC_{0-\infty}$: area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration
- V_d/F: apparent volume of distribution associated with the terminal slope, calculated, if feasible, as $Dose/(AUC_{0-\infty}*K_{el})$
- Cl/F: apparent total body clearance, calculated, if feasible, as $Dose/AUC_{0-\infty}$
- MRT: Mean residence time calculated, if feasible, as $AUMC_{0-\infty}/AUC_{0-\infty}$, were $AUMC_{0-\infty}$ is area under the moment concentration-time curve extrapolated to infinity

After multiple dose (day 14):

- C_{max_ss}: maximum safinamide plasma concentration at steady-state
- t_{max_ss}: time to achieve $C_{max,ss}$
- C_{min_ss}: trough safinamide plasma concentration at steady-state, measured as concentration at 24h
- $AUCss_{0-t}$: area under the concentration-time curve at steady-state from the last dose administration to the last observed concentration time t, calculated with the linear up/log down trapezoidal method
- $AUCss_{0-24}$: area under the concentration-time curve at steady-state in the tau interval (from the last dose administration to 24 h post dose), calculated with the linear up/log down trapezoidal method
- C_{ave_ss}: average safinamide plasma concentration at steady-state, calculated as AUC_{ss0-24} /tau
- R: accumulation ratio, calculated as AUC_{ss0-24}/ Day 8 AUC_{0-24}
- DF%: peak-trough fluctuation over one dosing interval at steady-state, calculated as $(C_{max,ss} - C_{min,ss})/C_{ave,ss}*100$
- $V_{d,ss}/F$: apparent volume of distribution at steady-state associated with the terminal slope, calculated, if feasible, as $Dose/(AUCss_{0-24}*K_{el})$
- Cl_{ss}/F: apparent total body clearance at steady-state, calculated, if feasible, as $Dose/ AUCss_{0-24}$

Secondary variables - Safety and tolerability:

- Treatment emergent adverse events, vital signs (blood pressure, heart rate), body weight, physical examinations, clinical laboratory parameters, ECG.

Analytics: Plasma samples for safinamide determination will be collected 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**);
- pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (**day 8**)
- pre-dose on **days 10, 11, 12, 13**.

Analyses will be performed at a certified bioanalytical laboratory (to be designated). The analytical method will be detailed in the study analytical plan. Analytical facilities and procedures will be in compliance with the general principles of GLP regulations.

Safety evaluation: Safety of the study treatments will be evaluated on the basis of treatment-emergent adverse events, clinical safety laboratory tests, vital signs, ECGs, and physical examinations.
Adverse events will be collected throughout the study. Vital signs will be measured at screening, during the study and at final visit or early termination visit (ETV) in case of discontinuation. Physical examinations, ECGs and clinical laboratory tests will be performed at screening and final visit/ETV.

Sample size: Twelve (12) healthy male and female Chinese volunteers per 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 (1).

Main selection criteria:

Inclusion criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males and females, 18-45 year old inclusive
3. *Ethnicity:* Chinese

STUDY SYNOPSIS (cont.)

Main selection criteria, continued: Inclusion criteria, continued:

4. *Weight:* body weight ≥ 50 kg;
5. *Body Mass Index*: 19-26 kg/m^2 inclusive
6. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting/supine position
7. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. *No nicotine addiction (smoker subjects only)*: ability to abstain for smoking for the duration of the clinical study
9. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception during the study and two weeks post-dose:
   a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
   b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   c. A male sexual partner who agrees to use a male condom with spermicide
   d. A sterile sexual partner

   Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.
   For all women, pregnancy test result must be negative at screening and day -1.

Exclusion criteria:

1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; positive result on HIV, hepatitis B, (HBV) (except for vaccination), hepatitis C (HCV). Retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
6. *Medications*: medications, including over the counter medications, herbal remedies and traditional Chinese remedies for 2 weeks before the start of the study. In particular statins and HMG-CoA reductase inhibitors in the 2 weeks before the screening visit; medicinal products that are BCRP substrates; treatment with morphine or other similar opioids, whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives and antiepileptic drugs in the 4 weeks before the screening visit; treatment with any known enzyme inhibiting or inducing agent within 4 weeks preceding the screening visit. Hormonal contraceptives for women will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study
8. *Blood donation*: blood donations or blood components transfusion for 3 months before this study
9. *Abuse drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes or equivalent amount of tobacco per day within 3 months prior to day -1)
10. *Abuse drug test*: positive result at urine drug test at screening or day-1
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians; consumption of grapefruit or products containing grapefruit within 48 hours prior to the enrolment; consumption of beverages containing xanthines (e.g. coffee, tea, soda, coffee, milk, energy drinks) within 48 hours prior to the enrolment
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

STUDY SYNOPSIS (cont.)

Schedule:
Procedures and assessments during study visits are listed in the table below:

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Subjects' screening number assignment ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications check ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Clinical laboratory analyses: haematology, blood chemistry, urinalysis, serum virology and serum pregnancy test (women) ➢ Urine multi-drug kit test ➢ Adverse events check ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	
Period 1 **Cohorts 1 and 2 - Visit 2**	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Urine pregnancy test (women) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subjects' randomisation number assignment ➢ Adverse events and concomitant medications check	<u>Day -1</u> Arrival at the clinical centre in the evening. Confinement until the morning of day 3. Standardised dinner Fasting for at least 10 h (overnight)
Period 1 **Cohorts 1 and 2 - Visit 3**	*Days 1 - 3*	<u>Day 1</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose <u>Day 1 - Day 3</u> ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose ➢ AEs and concomitant medications check	<u>Day 1</u> Standardised lunch at approximately 5 h post-dose. Standardised dinner at approximately 13 h post-dose. <u>Day 2</u> Standardised breakfast, lunch and dinner <u>Day 3</u> Discharge from the clinical centre in the morning after the 48-h blood sampling for PK analysis

STUDY SYNOPSIS (cont.)

Study schedule, continued:			
Period 1 Cohorts 1 and 2 - Visit 4	*Days 4 - 5* *Ambulatory visits*	Days 4 - 5 ➢ Blood sample collection for pharmacokinetic analysis at 72 h (day 4) and 96 h (day 5) post-dose ➢ Vital signs measurement at 96 h (day 5) post-dose ➢ AEs and concomitant medications check	Days 4 - 5 The subjects will return to the clinical centre each day in the morning for ambulatory blood sampling and safety checks Day 5 Subjects will be reminded to return to the clinical centre in the morning of day 8 for study Period 2.
A wash-out of 7 days will elapse between the single dose administered on day 1 and the first multiple dose administered on day 8			
Period 2 Cohorts 1 and 2 - Visit 5	*Days 8 -9*	Day 8 - Day 9 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ AEs and concomitant medications check Day 8 only ➢ Vital signs measurement at pre-dose and 2 h post-dose	Days 8-9 Subjects will be confined from the morning of day 8 (before investigational product administration) up to the morning of day 9. Subjects will be discharged after the 24-h blood sampling for PK analysis Day 8 Standardised lunch at approximately 5 h post-dose; Standardised dinner at approximately 13 h post-dose
Period 2 Cohorts 1 and 2 - Visit 6	*Days 10 - 13* *Ambulatory visits*	Days 10 - 13 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at pre-dose on each day ➢ Vital signs measurement before blood sampling and investigational product administration ➢ AEs and concomitant medications check	Days 10 - 13 The subjects will return to the clinical centre each day in the morning for ambulatory pre-dose blood sampling for PK analysis, investigational product administration and safety checks

STUDY SYNOPSIS (cont.)

Period 2 **Cohorts 1 and 2 - Visit 7**	*Days 14 - 17*	Day 14 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose Day 14 - Day 17 ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose ➢ AEs and concomitant medications check	Day 14 Standardised lunch at approximately 5 h post-dose. Standardised dinner at approximately 13 h post-dose Days 15-16 Standardised breakfast, lunch and dinner. Day 17 Discharge from the clinical centre in the morning after the 72-h blood sampling for PK analysis
Period 1 **Cohorts 1 and 2 - Visit 8**	*Day 18* *Ambulatory visit*	Day 18 ➢ Blood sample collection for pharmacokinetic analysis at 96 h post-dose ➢ Vital signs measurement at 96 h post-dose ➢ AEs and concomitant medications check Final visit assessments (see below) and discharge	Day 18 The subjects will return to the clinical centre in the morning for ambulatory blood sampling and safety checks Subjects will be discharged after final visit assessments (see Final visit/ETV below)
Final Visit/ETV	*Day 18. At ETV in case of early termination*	The following final assessments will be performed after the 96-h time-point assessments (day 18) or at ETV in case of early discontinuation: ➢ Physical examination (body weight, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis Vital signs assessments performed at 96 h post-dose on day 18 will be considered as the final assessment. Vital signs will also be measured at ETV, in case of early discontinuation. AEs and concomitant medications will also be checked at final visit/ETV. AEs will be captured up to the end of study visit. In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

STUDY SYNOPSIS (cont.)

Life style and constraints:

During the study, the subjects will be confined as follows:

- *from the evening preceding the first administration (study day -1) until the morning of day 3.*
- *from the morning of day 8 to the morning of day 9.*
- *from the morning of day 14 to the morning of day 17.*

Subjects will be discharged from the study after final assessments, as specified above (Final visit/ETV).
The subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before investigational product administration. On days 1, 8 and 14, subjects will remain fasted up to 5 h post-dose. Standardised meals will be served at the clinical centre according to the schedule above. Water will be allowed as desired, except for one hour before and one hour after investigational product administration. Coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement starting 48 h before the first administration until the end of the study. Smoking is not allowed for the whole study duration. Routine ambulant daily activities will be strongly recommended. Hazardous, strenuous or athletic activities will not be permitted.

Data analysis:

The data documented in this trial and the clinical parameters measured will be analysed using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.

Analysis set:

Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics

Safety set: all subjects who receive at least one dose of investigational medicinal product. This analysis set will be used for the safety analyses

PK set: all randomised subjects who fulfil the study protocol requirements in terms of investigational medicinal products intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the PK analysis

Safety Assessments:

The statistical analysis of demographic and safety data will be performed using SAS®.
The safety and tolerability of the investigational products will be evaluated on the basis of treatment-emergent adverse events occurrence, laboratory tests and other safety assessments (see section above).
All adverse events, adverse drug reactions (ADR) and serious adverse events (SAEs), if applicable, will be coded using the Medical Dictionary for regulatory Activities and summarized by system organ class and preferred term, incidence, severity and relationship to study drug.

Pharmacokinetics:

The pharmacokinetic parameters will be calculated with a Non-Compartmental Analysis (NCA) using Phoenix WinNonlin v6.3 (or higher). Pharmacokinetic data will be listed and summarised by descriptive statistics.

Study duration:

Maximum study duration for both cohort 1 and 2 will be 32 days including screening period, study Period 1, washout and study Period 2.

2 STUDY SCHEDULE (A MORE DETAILED TABLE IS SHOWN IN APPENDIX 1)

ACTIVITIES		Period 1			Period 2				Final visit/ETV[1]
	Screening	Single Dose			Multiple Dose				
Visit	V1	V2	V3	V4	V5	V6	V7	V8	
Day	Day -14/-2	Day -1	Day 1/3	Day 4/5	Day 8/9	Day 10/13	Day 14/17	Day 18	Day 18[2]
Informed consent	x								
Demography	x								
Lifestyle	x								
Medical and surgical history	x								
Physical examination[3]	x								x
Prior and concomitant medications	x	x	x	x	x	x	x	x	x
Height	x								
Body Weight[3]	x								x
Laboratory analysis[4]	x								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	x	x	x
Alcohol breath test		x							
Urine pregnancy test (women)		x							
ECG[6]	x								x
Inclusion/exclusion criteria	x	x							
Subject eligibility	x	x							
Enrolment and randomisation		x							
Confinement		x	x		x		x		
Discharge			x (day 3)		x (day 9)		x (day 17)		
Ambulatory visits				x		x		x	
Investigational product administration			x[7] (day 1)		x[7]	x[7]	x[7] (day 14)		
Blood sampling for PK analysis			x[8]	x[8]	x[9]	x[10]	x[8]	x[8]	
Standardised meals[11]		x	x		x		x		
Adverse event monitoring[12]	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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LIST OF ABBREVIATIONS

β-HCG	human chorionic gonadotropin β
γ-GT	γ-Glutamyl transpeptidase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOAC	Attributable-Legible-Contemporaneous-Original-Accurate-Complete
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from time zero to time t
$AUCss_{0-t}$ or $AUC_{0-t,ss}$	Area under the concentration-time curve at steady state
$AUC_{0-\infty}$	Area under the concentration vs. time curve up to infinity
AUC_{0-24h}	Area under the concentration-time curve in the tau interval
$AUCss_{0-24}$ or $AUC_{0-24h,ss}$	Area under the concentration-time curve at steady state in the tau interval
BUN	Blood Urea Nitrogen
BCRP	Breast Cancer Resistance Protein
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cl/F	Apparent total body clearance
C_{ave_ss}	Average drug concentration at steady state
C_{max}	Maximum drug concentration
C_{max_ss}	Maximum drug concentration at steady state
C_{mix_ss}	Trough drug concentration at steady state
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically Significant
CV	Coefficient of Variation
DF%	Peak-trough fluctuation over one dosing interval at steady-state
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IUD	Intra-Uterine Device
K_{el}	Terminal elimination rate constant
LLOQ	Lower Limit of Quantification
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit
MAO	Monoamino oxidase
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration

MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MW	Molecular Weight
N	Normal
NA	Not Applicable
NC	Not calculated
NCS	Not clinically significant
OTC	Over The Counter
PD	Parkinson's disease
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R_{acc}	Accumulation ratio
RBC	Red Blood Cells
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SNRI	Serotonin–norepinephrine reuptake inhibitors
SOC	System Organ Class
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test
T1	Xadago® 50 mg
T2	Xadago® 50 mg
TEAE	Treatment-Emergent Adverse Event
THC	Delta-9-tetrahydrocannabinol
$t_{1/2}$	Apparent terminal elimination half-life
t_{max}	Time to achieve C_{max}
V_d/F	Apparent volume of distribution associated with the terminal slope
WBC	White Blood Cells
WHODDE	World Health Organisation Drug Dictionary Enhanced

4 INTRODUCTION

4.1 Safinamide

4.1.1 Background

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 authorisation 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).

Safinamide uniquely combines potent, selective and reversible inhibition of monoamino oxidase B (MAO-B) with blockade of voltage-dependant Na^+ and Ca^{2+} channels and inhibition of glutamate release (4,8), thus showing a novel mode of action, targeting both dopaminergic and glutaminergic systems (9,10).
Data from Phase III clinical studies gave evidence that safinamide 50 or 100 mg/day improves the motor function in Parkinson's disease when prescribed as add-on therapy to dopamine agonists or L-dopa (3).

4.1.2 Clinical pharmacology and pharmacokinetics

Safinamide pharmacokinetics after single and multiple dose administrations have been described (11,12). At single ascending oral doses ranging from 2.5 to 10.0 mg/kg, safinamide was absorbed in a linear and dose-proportional fashion. Peak plasma levels were obtained on average at 1.8 to 2.8 h post-dose. Concentrations declined with a terminal half-life of 20 - 23h (11,12). Absolute bioavailability is high (95%), showing that safinamide is almost completely absorbed after oral administration and first pass metabolism is negligible (SmPC, 3). A complete long-lasting inhibition of platelet MAO-B activity was observed at all doses tested. Food intake prolonged the rate but did not affect the extent of safinamide absorption (11,12).
Studies in healthy volunteers (13,15) demonstrated that safinamide does not affect oral tyramine metabolism mostly mediated by the intestinal MAO-A, and confirm that it can be administered without tyramine-related dietary restrictions.

4.1.3 Safety

The overall safety profile of Xadago® is based on the clinical development program performed on over 3000 subjects, of which over 600 were treated for more than 2 years.

The most common side effects related to safinamide are dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension. Serious adverse reactions, such as hypertensive crisis (high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, CPK increase), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension, are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors.

With MAO-inhibitors there have been reports of drug interactions with concomitant use of sympathomimetic medicinal products. Impulse control disorders, pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments.

A complete list of adverse reactions observed with safinamide is presented in the SmPC (3).

4.2 Study rationale

The present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations (1).

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.

4.3 Risks and benefits

For AEs occurred with safinamide in previous clinical studies, please refer to § 4.1.3 and the SmPC (3). The most common side effects are dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension.

Based on the clinical experience, no particular risks are expected for the study subjects considering safinamide 50 mg and 100 mg multiple dose administrations.

5 STUDY OBJECTIVES

The objective of the study is to evaluate safinamide pharmacokinetic profile, safety and tolerability after single and multiple dose administration to healthy adult Chinese volunteers

5.1 Primary end-point

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

5.2 Secondary end-point

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

6 CLINICAL SUPPLIES

6.1 Treatment

6.1.1 Description of investigational products

TEST PRODUCT 1 (T1)	
Name	Xadago® 50 mg film-coated tablets
Active ingredient	Safinamide methanesulphonate (corresponding to 50 mg safinamide)
Marketing Authorization Holder	Zambon S.p.A., Italy
Pharmaceutical form	Film-coated tablets
Dose	Single 50 mg dose on day 1 Multiple 50 mg doses, once daily, for 7 days
Administration route	Oral

TEST PRODUCT 2 (T2)	
Name	Xadago® 100 mg film-coated tablets
Active ingredient	Safinamide methanesulphonate (corresponding to 100 mg safinamide)
Marketing Authorization Holder	Zambon S.p.A., Italy
Pharmaceutical form	Film-coated tablets
Dose	Single 100 mg dose on day 1 Multiple 100 mg doses, once daily, for 7 days
Administration route	Oral

6.1.2 Dose regimen

Subjects will be randomised 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 randomised, parallel-group design, as follows:

- Cohort 1: One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets administered o.d. from day 8 to day 14.

- Cohort 2: One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 100 mg film-coated tablets administered o.d. from day 8 to day 14.

Dose regimens are also summarised in the scheme below:

Table 6.1.2.1 Study dose regimen

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

6.1.3 Route and method of administration

The investigational products will be orally administered in the morning, at 8:00±1h, under fasting conditions, with 240 mL (total volume) of still mineral water.

A mouth-and-hand check will be performed immediately after dosing to ensure treatment compliance.

6.1.4 Investigational product distribution

All doses of the investigational products will be administered at the clinical centre by the investigator or by his/her deputy. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

6.2 Packaging and labelling

Packaging and labelling for the clinical study will be performed by a GMP compliant vendor, delegated by Zambon S.p.A., Italy.

Subjects' kit labelling will report all the information according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4, 16), as follows:

a. Name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical study)
b. Pharmaceutical dosage form, route of administration, quantity of dosage units, and the name/identifier and strength/potency
c. The batch and/or code number to identify the contents and packaging operation
d. A study reference code allowing identification of the study, site, investigator and sponsor if not given elsewhere
e. A blank space for subject enrolment Nr. (to be reported by hand by the Investigator) and where relevant, the visit number
f. The name of the investigator (if not included in (a) or (d))
g. Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)
h. “For clinical study use only” or similar wording

i. The storage conditions

j. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity

k. "Keep out of reach of children"

The label will be in Chinese language.

6.3 Storage conditions

The investigational products will be stored at ≤ 25° C in a dry locked place, sheltered from light.

6.4 Drug accountability

The vendor delegated by Zambon S.p.A., Italy, will provide the clinical centre with a sufficient number of individual subject kits to conduct the study, plus sufficient reserve kits.

After receipt of the drug supply, the Pharmacist will confirm in writing by signing and dating standard drug accountability forms. At the end of the study, the drug product will be maintained in the original containers.

At the end of the study, used, unused and partially used supplies of the investigational products, provided by the vendor delegated by Zambon S.p.A., Italy, will be stored as detailed in § 6.3 above and then disposed of (upon sponsor written authorisation), after assessment of drug accountability.

7 INVESTIGATIONAL PLAN

7.1 Overall study design

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

7.2 Discussion of design

Following a specific request of CFDA, the present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations (1).

Safinamide has recently been granted marketing authorization in EU, Norway and Switzerland on the basis of the results of clinical trials performed in European countries. 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.

Two single doses (i.e. 50 and 100 mg) of safinamide will be administered to two subject' cohorts. The study will continue with multiple administrations of safinamide 50 and 100 mg, orally taken once a day for 7 days.

The 50 and 100 mg oral doses have been selected according to the common clinical practice (see Xadago® SmPC). These doses were investigated in the previously performed Phase III clinical trials. The volunteers will be assigned to the two cohorts according to the study randomised, parallel-group design.

Safinamide pharmacokinetic profile will be investigated after single dose, according to CFDA guidance requirements, and at steady state since multiple doses are administered in the clinical practice. Safinamide steady state should be reached after 5 or 6 days of treatment (day 13-14 in this study). Safinamide pre-dose concentrations will be assessed before the last 5 doses (days 10-14).

An open design was chosen. However, no bias on study outcome is expected considering that the study PK endpoints are based on the objective measurement of safinamide in plasma.
Blood sampling time-points were selected on the basis of the known PK profile of safinamide. The sampling time lasts for about 4-7 elimination half-lives (mean PK half-life: 20-23 h) after both single dose and the last multiple dose administration.

8 STUDY POPULATION

8.1 Target population

Twenty-four (24) healthy male and female Chinese volunteers, aged 18-45 years inclusive, will be enrolled into the study.

8.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all these criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males and females, 18-45-year old inclusive
3. *Ethnicity:* Chinese
4. *Weight:* body weight ≥ 50 kg;
5. *Body Mass Index*: 19-26 kg/m^2 inclusive
6. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting/supine position
7. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. *No nicotine addiction (smoker subjects only)*: ability to abstain for smoking for the duration of the clinical study
9. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception during the study and two weeks post-dose:
    a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
    b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
    c. A male sexual partner who agrees to use a male condom with spermicide
    d. A sterile sexual partner

    Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.
    For all women, pregnancy test result must be negative at screening and day -1.

8.3 Exclusion criteria

Subjects meeting any of these criteria will not be enrolled in the study:

1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study

3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; positive result on HIV, hepatitis B (HBV) (except for vaccination), hepatitis C (HCV). Retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
6. *Medications*: medications, including over the counter medications, herbal remedies and traditional Chinese remedies for 2 weeks before the start of the study. In particular statins and HMG-CoA reductase inhibitors in the 2 weeks before the screening visit; medicinal products that are BCRP substrates; treatment with morphine or other similar opioids, whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives and antiepileptic drugs in the 4 weeks before the screening visit; treatment with any known enzyme inhibiting or inducing agent within 4 weeks preceding the screening visit. Hormonal contraceptives for women will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study
8. *Blood donation*: blood donations or blood components transfusion for 3 months before this study
9. *Abuse drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes or equivalent amount of tobacco per day within 3 months prior to day-1)
10. *Abuse drug test*: positive result at urine drug test at screening or day-1
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians; consumption of grapefruit or products containing grapefruit within 48 hours prior to the enrolment; consumption of beverages containing xanthines (e.g. coffee, tea, soda, coffee, milk, energy drinks) within 48 hours prior to the enrolment
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

8.3.1 Not allowed treatments

No medication, including OTC, herbal remedies and traditional Chinese remedies, will be allowed for 2 weeks before the start of the study and during the whole study duration.

Statins and HMG-CoA reductase inhibitors use will not be allowed for 2 weeks before and during the study. Wash-out interval for the treatment with morphine or other similar opioids,

whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives, antiepileptic drugs and the treatment with any known enzyme inhibiting or inducing agent or any investigational drugs intake will be at least 4 weeks before the screening visit. Hormonal contraceptives are allowed.

Paracetamol will be allowed as therapeutic counter-measure for adverse events (AEs) according to the investigator's opinion. The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the investigator, together with the sponsor, considers it could affect the study assessments or outcome.

9 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

9.1 Study visits and procedures

Each study subject completing the study will undergo 8 visits plus a final visit.

The study protocol foresees 2 periods: in the first one the investigational products are administered in single dose, in the second one in multiple doses. The single dose in the first period and the first dose in the second period are separated by a wash-out interval of 7 days. Maximum and minimum study duration will be 32 and 20 days, respectively, screening visit included.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical centre by the 1st screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the clinical centre (or a telephonic follow-up, if applicable) by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – visit 1: between day -14 and day -2
  - Period 1 – visit 2: day -1

- **Interventional phase**
  - Period 1 – visit 3: days 1-3: single dose and blood sampling for PK analysis
  - Period 1 – visit 4: days 4-5: ambulatory visits - blood sampling for PK analysis
  - Wash-out interval of 7 days
  - Period 2 – visit 5: days 8-9: first multiple dose and blood sampling for PK analysis
  - Period 2 – visit 6: days 10-13: ambulatory visits - multiple doses and blood sampling for PK analysis
  - Period 2 - visit 7: days 14-17: last multiple dose and blood sampling for PK analysis
  - Period 2 - visit 8: day 18: blood sampling for PK analysis

- **Final phase**
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)

Study schedule

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Subjects' screening number assignment ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications check ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Clinical laboratory analyses: haematology, blood chemistry, urinalysis, serum virology and serum pregnancy test (women) ➢ Urine multi-drug kit test ➢ Adverse events check ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	
Period 1 Cohorts 1 and 2 - Visit 2	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Urine pregnancy test (women) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subjects' randomisation number assignment ➢ Adverse events and concomitant medications check	<u>Day -1</u> Arrival at the clinical centre in the evening Confinement until the morning of day 3. Standardised dinner Fasting for at least 10 h (overnight)
Period 1 Cohorts 1 and 2 - Visit 3	*Days 1 - 3*	<u>Day 1</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose <u>Day 1 - Day 3</u> ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose ➢ AEs and concomitant medications check	<u>Day 1</u> Standardised lunch at approximately 5 h post-dose. Standardised dinner at approximately 13 h post-dose <u>Day 2</u> Standardised breakfast, lunch and dinner <u>Day 3</u> Discharge from the clinical centre in the morning after the 48-h blood sampling for PK analysis

Study schedule, continued

Period 1 **Cohorts 1 and 2 - Visit 4**	*Days 4 - 5* *Ambulatory visits*	Days 4 - 5 ➢ Blood sample collection for pharmacokinetic analysis at 72 h (day 4) and 96 h (day 5) post-dose ➢ Vital signs measurement at 96 h (day 5) post-dose ➢ AEs and concomitant medications check	Days 4 - 5 The subjects will return to the clinical centre each day in the morning for ambulatory blood sampling and safety checks Day 5 Subjects will be reminded to return to the clinical centre in the morning of day 8 for study Period 2.
A wash-out of at least 7 days will elapse between the single dose administered on day 1 and the first multiple dose administered on day 8			
Period 2 **Cohorts 1 and 2 - Visit 5**	*Days 8 -9*	Day 8 - Day 9 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ AEs and concomitant medications check Day 8 only ➢ Vital signs measurement at pre-dose and 2 h post-dose	Days 8-9 Subjects will be confined from the morning of day 8 (before investigational product administration) up to the morning of day 9. Subjects will be discharged after the 24-h blood sampling for PK analysis Day 8 Standardised lunch at approximately 5 h post-dose; Standardised dinner at approximately 13 h post-dose
Period 2 **Cohorts 1 and 2 - Visit 6**	*Days 10 - 13* *Ambulatory visits*	Days 10 - 13 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at pre-dose on each day ➢ Vital signs measurement before blood sampling and investigational product administration ➢ AEs and concomitant medications check	Days 10 - 13 The subjects will return to the clinical centre each day in the morning for ambulatory pre-dose blood sampling for PK analysis, investigational product administration and safety checks

Study schedule, continued

Period 2 **Cohorts 1 and 2 - Visit 7**	*Days 14 - 17*	Day 14 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose Day 14 - Day 17 ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose ➢ AEs and concomitant medications check	Day 14 Standardised lunch at approximately 5 h post-dose. Standardised dinner at approximately 13 h post-dose Days 15-16 Standardised breakfast, lunch and dinner. Day 17 Discharge from the clinical centre in the morning after the 72-h blood sampling for PK analysis
Period 1 **Cohorts 1 and 2 - Visit 8**	*Day 18* *Ambulatory visit*	Day 18 ➢ Blood sample collection for pharmacokinetic analysis at 96 h post-dose ➢ Vital signs measurement at 96 h post-dose ➢ AEs and concomitant medications check Final visit assessments (see below) and discharge	Day 18 The subjects will return to the clinical centre in the morning for ambulatory blood sampling and safety checks. Subjects will be discharged after final visit assessments (see Final visit/ETV below)
Final Visit/ETV	*Day 18. At ETV in case of early termination*	The following final assessments will be performed after the 96-h time-point assessments (day 18) or at ETV in case of early discontinuation: ➢ Physical examination (body weight, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis Vital signs assessments performed at 96 h post-dose on day 18 will be considered as the final assessment. Vital signs will also be measured at ETV, in case of early discontinuation. AEs and concomitant medications will also be checked at final visit/ETV. AEs will be captured up to the end of study visit. In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

9.2 Diet, lifestyle and study restrictions

During the study, the subjects will be confined at the clinical centre as follows:

Period 1:
- from the evening preceding the first administration (study day -1) until the morning of day 3.

Period 2:
- from the morning of day 8 to the morning of day 9.
- from the morning of day 14 to the morning of day 17.

Subjects will be discharged from the study after final assessments (Final visit or ETV).

The subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before investigational product administration. On days 1, 8 and 14, subjects will remain under fasting conditions up to 5 h post-dose.
Standardised meals will be served at the clinical centre according to the schedule below:

- 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 and Days 15/16: standardised breakfast, lunch and dinner

Water will be allowed as desired, except for 1 h before and 1 h after investigational product administration. Coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement starting 48 h before the first administration until the end of the study. Smoking is not allowed for the whole study duration.

Routine ambulant daily activities will be strongly recommended. Hazardous, strenuous or athletic activities will not be permitted.

10 DESCRIPTION OF SPECIFIC PROCEDURES

10.1 Physical examination

Full physical examinations will be performed at screening and final visit/ETV. Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs.
All clinically significant abnormalities after the screening visit will be recorded as AEs.

10.1.1 Body weight

Body weight will be recorded at screening and final visit/ETV.
Subjects will be weighed (kg) lightly clothed without shoes. Height will be measured at screening only and Body Mass Index (BMI) will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

10.1.2 Vital signs

Subjects' blood pressure and heart rate will be measured by the investigator or his deputy after 5 min at rest (sitting/supine position) at the following times:

- at screening
- on day 1, day 8 and day 14: at pre-dose and 2 h post-dose
- on day 5 and day 18: at 96 h post-dose
- on days 10-13: at pre-dose
- at ETV (if applicable).

10.1.3 ECGs

12-Leads ECGs will be performed (supine position) at screening and final visit/ETV.

Date/time of the ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. Hard copies of the ECGs will be attached to the CRF.

10.2 Clinical laboratory assays

Samples of blood and urine will be collected. The following laboratory analyses will be performed at the screening visit:

HAEMATOLOGY
Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, haemoglobin (conv. units), haemoglobin (IS units), haematocrit, MCV, MCH, MCHC, thrombocytes.

BLOOD CHEMISTRY
Electrolytes: sodium, potassium, calcium, chloride, inorganic phosphorus
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: total bilirubin, creatinine, glucose, urea or BUN, uric acid, total cholesterol, triglycerides
Proteins: total proteins

Serum pregnancy test (women).

URINE ANALYSIS
Urine chemical analysis (stick)**:** pH, specific weight, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, haematic pigments, leukocytes
Urine sediment (analysis performed only if sediment is present): leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria

SERUM VIROLOGY
Hepatitis B (HBs antigen), **Hepatitis C** (HCV antibodies), **HIV 1/2** (HIV Ag/Ab combo).

A urine drug test will be performed at the clinical centre at screening, using a urine multi-drug kit. The following drugs will be assessed: cocaine, amphetamine, morphine, cannabis, benzodiazepines, barbital.

A serum pregnancy test will be performed by the laboratory at screening, as listed above. Urine pregnancy test will be performed on day -1 of each study period at the clinical centre.

The same analyses, with the exception of urine drug test, virology and pregnancy test, will be performed at the final visit/ETV.

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be reported in the individual eCRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs.

10.3 Sampling for pharmacokinetic analysis

10.3.1 Venous blood sampling

Venous blood samples (up to 10 mL) will be collected from a forearm vein at the following times:

- At pre-dose (0 h), 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 (days 1-5) and the last multiple dose (days 14-18)
- At pre-dose on days 10-13
- At pre-dose (0 h) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (days 8-9)

Actual sampling times for each subject will be recorded in the individual CRFs. The actual sampling times should not exceed the recommended tolerance ranges presented in the following table. Any deviation outside the recommended ranges will be verified through Data Clarification Forms and, if confirmed, will be reported as protocol deviation, although it will not automatically lead to the exclusion of the concerned subjects from the PK set.

Table 10.3.1.1 Tolerance ranges for the scheduled sampling times

Sampling time	Tolerance range
Pre-dose (0)	Within 30 minutes before investigational product administration
0.5 h (30 min)	± 1 min
1, 1.5 h	± 3 min
2, 3, 4 h	± 5 min
6, 8, 10, 12, 16, 24, 36, 48, 72, 96 h	± 10 min

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20 I.U./mL Na-heparin. The first 2 mL of blood will be discarded at each collection time to avoid contamination of the sample with heparin.

The remaining 8 mL will be collected from the catheter and transferred with a syringe into heparinised tubes (Li-heparin).
Samples handling and processing is described in study specific lab manual.

10.3.2 Analytics

The concentration of safinamide in plasma samples will be determined at a certified analytical laboratory (to be designated). Analyses will be performed according to the general Principles of “OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and GCP.

The method validation report and the analytical report will be attached to the final report.

10.3.3 Labelling, storage and transport of samples

10.3.3.1 Samples labelling

Labels and labelling process are described in the study specific lab manual.

10.3.3.2 Samples storage and transport

During the study the samples will be stored at ≤- 70° C. At the end of each collection day, aliquots 1 and 2 will be stored in separate freezers.

All aliquots 1, packed in sufficient dry ice, will be shipped by an authorised courier from the clinical centre (China) to the analytical laboratory.

11 ASSIGNMENT OF STUDY TREATMENT

11.1 Randomisation

Randomisation will be used to minimize bias in the assignment of subjects to treatment cohorts, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) will be evenly balanced across treatment cohorts.
The randomisation schedulewill be computer-generated by the CRO biostatistician using SAS®.
The randomisation schedulewill be attached to the final clinical study report.

11.2 Treatment allocation

Subjects will be randomised 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 randomised, parallel-group design.

On day -1, Period 1, subjects will be assigned a randomisation number, which will be used to assign the study treatment according to the randomisation schedule, as detailed above.
Subjects who prematurely discontinue participation after randomisation will not be replaced.

11.3 Blinding

This is an open study. No masking procedure will be applied.
The open label design is considered appropriate for the primary objective of pharmacokinetic characterization, because PK properties and assessments are not prone to bias of observation by the investigators or the subjects.

12 EVALUATION PARAMETERS

12.1 Study variables

12.1.1 Primary variables

The following safinamide PK parameters will be determined on day 1 (after the first dose), on day 8 (after the first multiple dose) and on day 14 (after the last dose):

After single dose and first multiple dose (day 1 and day 8)

- C_{max}, t_{max}, AUC_{0-t}, and AUC_{0-24h}

After single dose only (day 1):

- K_{el}, $t_{1/2}$, $AUC_{0-\infty}$, V_d/F, Cl/F and MRT

After multiple dose (day 14):

- C_{max_ss}, t_{max_ss}, C_{min_ss}, $AUC_{0-t,ss}$, $AUC_{0-24h,ss}$, C_{ave_ss}, R_{acc}, DF%, $Vd_{,ss}/F$ and $Cl_{,ss}/F$

12.1.2 Secondary variables

- Treatment emergent adverse events (TEAEs), vital signs (blood pressure, heart rate), body weight, physical examinations, clinical laboratory parameters, ECG.

12.2 Pharmacokinetic assessments

12.2.1 Pharmacokinetic parameters

The following safinamide PK parameters will be measured and/or calculated with a Non-Compartmental Analysis (NCA) using Phoenix WinNonlin v6.3 (or higher).

After single dose and first multiple dose (day 1 and day 8):

C_{max}:	Maximum safinamide plasma concentration
t_{max}:	Time to achieve C_{max}
AUC_{0-t}:	Area under the concentration-time curve from single dose administration to the last quantifiable concentration time t
AUC_{0-24h}:	Area under the concentration-time curve in the tau interval (from single dose administration to 24 h post dose)

After single dose (day 1):

K_{el}:	Apparent terminal elimination rate constant, calculated, if feasible, from the slope of a log-linear regression using at least 3 last concentration > LLOQ points
$t_{1/2}$:	Apparent terminal elimination half-life, calculated, if feasible, as $\ln 2/K_{el}$
$AUC_{0-\infty}$:	Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable drug concentration
V_d/F:	Apparent volume of distribution associated with the terminal slope, calculated, if feasible, as $Dose/(AUC_{0-\infty}*K_{el})$

Cl/F:	Apparent total body clearance, calculated, if feasible, as Dose/$AUC_{0-\infty}$
MRT:	Mean residence time, calculated, if feasible, as $AUMC_{0-\infty}/AUC_{0-\infty}$, were $AUMC_{0-\infty}$ is area under the moment concentration-time curve extrapolated to infinity

The sampling schedule is considered adequate if the ratio $AUC_{0-t}/AUC_{0-\infty}$ equals or exceeds a factor of 0.8 (i.e. if $\%AUC_{extra}$ is <20%) for more than 80% of the individual PK profiles. This assures that AUC_{0-t} covers a sufficient percentage of the theoretical total extent of exposure.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a determination coefficient $R^2 \geq 0.8$. Individual extrapolated parameters, when considered unreliable, will be reported as NC (not calculated).

After multiple dose (day 14):

C_{max_ss}:	Maximum safinamide plasma concentration at steady state
t_{max_ss}:	Time to achieve C_{max-ss}
AUC_{0-t},ss:	Area under the concentration-time curve at steady state from the last dose administration to the last quantifiable concentration time t
AUC_{0-24h},ss:	Area under the concentration-time curve at steady state in the tau interval (from the last dose administration to 24 h post dose)
C_{ave_ss}:	Average safinamide plasma concentration at steady state, calculated as AUC_{0-24h},ss /tau (24 h)
R_{acc}:	Accumulation ratio, calculated as $AUC_{0-24h,ss}$/ AUC_{0-24h}
DF%:	Peak-trough fluctuation over one dosing interval at steady-state, calculated as $(C_{max,ss} - C_{min,ss})/C_{ave,ss}*100$
$V_{d,}/F_{ss}$	apparent volume of distribution at steady-state associated with the terminal slope, calculated, if feasible, as Dose/(AUC_{0-24h},ss*K_{el})
$Cl_{,}/F_{ss}$	apparent total body clearance at steady-state, calculated, if feasible, as Dose/ AUC_{0-24h},ss

12.3 Safety assessments

Safety and general tolerability of the investigational products will be based on TEAEs, physical examinations, including body weight, vital signs, ECGs and routine haematology, blood chemistry and urinalysis laboratory tests.

13 STATISTICAL METHODS

The data documented in this study and the parameters measured will be evaluated using classic descriptive statistics, i.e. geometric mean, geometric CV (%) (PK data only), arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using Statistical Analysis Software (SAS®) Version 9.3 or higher.
The pharmacokinetic parameters will be calculated using the actual recoded sampling times and non-compartmental methods with Phoenix WinNonlin (Version 6.3 or higher).

13.1 Analysis Sets

13.1.1 Definitions

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 enrolment will be performed through randomised allocation to a treatment cohort. An eligible but not enrolled subject will be defined as a reserve.
A subject will be defined as randomised in the study when he/she is assigned to a randomised treatment cohort.

The following analysis sets will be considered:

- Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics.
- Safety set: all randomised subjects who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for the safety analyses.
- PK set: all randomised subjects who fulfil the study protocol requirements in terms of investigational medicinal products intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the PK analysis.

Each subject will be coded as valid or not valid for the Randomised set, Safety set and PK set. Subjects will be evaluated according to the treatment they actually receive.

13.1.2 Reasons for exclusion from the PK set

Reasons for the exclusion of subjects from the PK set are the following:

Before bioanalysis

- vomiting and diarrhoea 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

If one of these events occurs, it will be noted in the CRF as the study is being conducted.

After bioanalysis

Exclusion of subjects on the basis of pharmacokinetic reasons is possible only for:

- subjects 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 $AUC_{0-\infty}$.
Any data excluded will be discussed in the CSR.

13.2 Sample size and power considerations

Twelve (12) healthy male and female Chinese volunteers / 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 (1).

13.3 Demographic, baseline and background characteristics

Demographic and background characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarised in contingency tables. Quantitative data will be summarised using classic descriptive statistics. The baseline will be the last pre-dose measurement.

13.4 Analysis of pharmacokinetic parameters

A descriptive PK will be presented. The results will be displayed and summarised in tables and figures. Individual and mean curves (+SD at nominal times), indicating inter-subject variability, will be plotted. Data below the lower limit of quantification (BLQ) will be

considered as 0 in the calculations and presented as BLQ in listings and tables. As a consequence of BLQ(i.e. 0) values, calculated geometric means (if requested) could be null. For this reason, in the presence of any null value, the geometric mean will be reported as not calculated (NC).

13.5 Safety and tolerability evaluation

13.5.1 Adverse events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).
AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of investigational product and not worsening after the first dose of investigational product.
- TEAEs: all AEs occurring or worsening after the first dose of investigational product

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship with investigational product and severity.

13.5.2 Physical examination

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed.

13.5.3 Laboratory data

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be listed. All laboratory results will be listed and a table of all the abnormal values will be presented.

13.5.4 Vital signs

Vital signs values will be listed and summarised by descriptive statistics.

13.5.5 Body weight

Body weight values will be listed and summarised by descriptive statistics.

13.5.6 ECG

Date/time of ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. Hard copies of the ECGs will be attached to the CRF.

14 DEFINITION AND HANDLING OF AEs AND SAEs

14.1 Applicable SOPs

AEs definition, classification and management will follow the CRO's SOPs, based upon applicable local and international regulations. The full SOPs or an operative summary will be made available in the CRO.

A brief summary of AE definition, classification and management is reported below.

14.2 Definition of Adverse Event (AE)

An Adverse Event is "*any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*".

AEs include:

- worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- patient/subject deterioration due to the primary illness
- intercurrent illnesses
- drug interactions
- events related or possibly related to concomitant medications
- abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

14.3 Definition of Adverse Drug Reaction (ADR)

An Adverse Reaction is "*any untoward and unintended response to an investigational medicinal product related to any dose administered*".
All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or matter to suggest a causal relationship.

- **Unexpected Adverse Drug Reaction**

An unexpected ADR is: "*An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (Reference Safety Information [RSI]).*

- **Reference Safety Information (RSI)**: in order to assess whether an adverse reaction is expected, the SmPC will be used.

14.4 Definition of Serious Adverse Events or Serious Adverse Drug Reaction

A Serious Adverse Event (SAE) is: "*any untoward medical occurrence or effect that at any dose*:

- results in death
- is life-threatening (i.e. the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but, according to appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

A **Serious Adverse Drug Reaction (SADR)** is an ADR that meets also the definition of SAE.

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is an ADR that is both unexpected (not consistent with the applicable product information, e.g. SmPC) and also meets the definition of a SAE.

A non-serious adverse event is any adverse event that does not meet the criteria listed above for a serious adverse event.

14.5 Definition of Severity of Adverse Events

The term "severe" is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the subject may experience slight discomfort.
- Moderate: causing some limitation of usual activities; the subject may experience annoying discomfort.
- Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

14.6 Definition of Adverse Event causality

Causality shall be determined according to the definition of ADR given in 14.3.

All AE judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor.

The following binary decision for causality will be used:

- Reasonable possibility that the IMP caused the event
- No reasonable possibility that the IMP caused the event

Features supportive of an association include:

- temporal plausibility
- pharmacological properties of the drug or of the substance class
- course of the adverse event after dechallenge and, if applicable, after rechallenge
- specific tests indicating involvement of the drug in the occurrence/worsening of the adverse event
- alternative explanations

14.7 Adverse Events recording

Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the investigator, whether believed by the investigator to be related or unrelated to the IMP, must be recorded on the AE information page of the CRF (for SAEs information must be recorded also on the "Serious Adverse Event Form").
The Investigator will also perform an evaluation with respect to seriousness and causality (relationship of any AE to IMP) of the AEs. and record it on the appropriate section of the CRF and on the "Serious Adverse Event Form" (if appropriate).

14.8 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: up to final study visit/ETV (observation window)

An AE occurring after the final visit/ETV and coming to knowledge of the investigator (e.g. during a follow-up assessment or by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator's judgment.

14.9 Adverse Events reporting

The official language for reporting is English. The investigator and clinical staff of the present study are familiar with English language.

The investigator must report to the CRO all AEs which occur during the study, regardless of their relationship to the IMP. Protocol specific AEs or laboratory abnormalities critical to safety

evaluations are to be identified in the protocol and reported to the sponsor according to reporting requirements and within the time periods specified.

All AEs are recorded by the investigator on the AE information page of the CRF.

In addition, SAE will have to be reported according to the following detailed procedure.

14.9.1 SAEs reporting

The investigator must report the SAEs to the CRO no later than 24 hours from when he/she becomes aware of the SAE, by Electronic Data Capture (preferred method), or e-mailing as scanned attachment (back up plan) or by faxing the "Serious Adverse Event Form" (back up plan) to the CRO, as stated in the "List of CRO/ personnel" in § 14.13 of this protocol.

The standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

Another copy of the "Serious Adverse Event Form " will be sent to the Medical Affairs/Clinical Operations for the Sponsor's file and another copy will be retained by the Investigator for the Investigator's file.

If the investigator becomes aware of any SAE occurred to a subject within the follow-up window established in the protocol, he/she will report the SAE as above. The SAE will be also reported in the CRF.

If outside the follow-up window established in the protocol the investigator becomes aware of a SAE, if the investigator judges that the SAE is related to the study drug, it should be reported to the Sponsor. The Investigator might use the "Serious Adverse Event Form" via email or fax, but the SAE must not to be reported in the CRF, as it is not an event occurred within the study period.

The investigator must report all SAEs that occur to the subjects to National Medical Products Administration/Local Ethics Committee/Provincial Food and Drug Administration/National Health and Family Planning Commission immediately no later than 24hours from when he/she becomes aware of SAE. Any SAEs that happen to the subjects outside the follow-up window should be reported by investigator to National Medical Products Administration/Local Ethics Committee/Provincial Food and Drug Administration/National Health and Family Planning Commission immediately.

14.10 Follow-up for Adverse Events

A follow-up "Serious Adverse Event Form" will be filled in if important follow-up information (i.e. diagnosis, outcome, causality assessment, results of specific investigations) is made available after submission of the initial AE Form for immediate reporting. Follow-up "Serious Adverse Event Form" will be reported to the Sponsor as above-described, under Section 14.9.1.

In any case of an AE that, in the opinion of the investigator, requires the subject's discontinuation, follow-up information relating to the subject's subsequent course must be collected until the event has subsided or the condition stabilised or when the subject is lost to follow up or death.

When follow-up data on non-serious AE are collected, information should be reported under "Comments" in the Final report of the CRF.

14.11 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the CRO/sponsor (day 0).
Fatal and life-threatening SUSARs, should be reported to Competent Authority as soon as possible and in any case within 7 days and to Ethics Committee per the requirement .
If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days. Complete follow-up report should be sent within 15 calendar days.
SUSARs which are not fatal and not life-threatening are to be reported to Competent Authority within 15 days and to Ethics Committee per the requirement.
The minimum information to be reported includes:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP (including active substance name, code)
- A causality assessment.

14.12 Other events qualified for expedited reporting

Other safety issues also qualify for expedited reporting may be sent to Competent authority when they might materially alter the current benefit-risk assessment of a medicinal product or would be sufficient to consider changes in the medicinal product administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the subject has completed a clinical trial and are reported to the investigator by the subject.
- new events relating to the conduct of the trial or the development of the medicinal product likely to affect the safety of the subjects, such as :
  - a SAE which could be associated with the trial procedures and which could modify the conduct of the trial

- a significant hazard to the subject population such as lack of efficacy of a medicinal product used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical trials.

14.13 SAEs: contacts

The investigator will report any SAE to the CRO. The CRO's details for SAEs are the following:
Email PPD

The sponsor's details for SAEs are the following:
Phone: PPD
Fax: PPD
Email: PPD

14.14 Pregnancy

Subjects must be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator, who must then withdraw the subject from the study without delay. The Investigator should also be notified of pregnancy occurring during the study but confirmed after its completion. In the event that a subject is subsequently found to be pregnant after inclusion in the study, then any pregnancy will be followed up to the end of pregnancy or pregnancy termination and the status of mother and child will be reported to the Sponsor after delivery through the Pregnancy Report Form provided by the Sponsor. The Investigator will send pregnancy reports to DSU within the timeframes of SAEs, with follow-up information to be actively sought for the outcome of pregnancy.

- Part I of the Form is completed at the time of awareness of foetal exposure during pregnancy.
- Part II of the Form is filled in when information on pregnancy outcome becomes available.

If pregnancy results in abnormal outcome (spontaneous miscarriage, stillbirth and congenital anomalies) will be considered as SAE. If the investigator considers this to be due to the IMP, this will be treated as an expedited ADR report.

15 DATA MANAGEMENT PROCEDURES

15.1 Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRFs. He/she must also check that the data reported in the eCRFs correspond to those in the subject's source documents.
ECG and laboratory results must be printed and signed by the Investigator and kept as source data on site after entering outcome into the eCRF.
All other data has to be documented in the subject file as source data first and then entered into the eCRF.
Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a subject visit, and monitors will have access to data recorded. These data will be reviewed

versus source documents by trial monitors for completeness and acceptability during monitoring visits.
If data correction is required for an eCRF after initial entry, the site personnel can make necessary corrections on their own or as a response to an automated query by the eCRF system. Monitor and Clinical Data Manager review the eCRF for accuracy and can also generate queries to the investigational staff for resolution.
Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

15.2 Database management

The CRO will update and verify the database and create the final SAS data sets. The final data file will be transferred to the sponsor in the agreed format with all the other study documentation.

15.2.1 Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities, AEs and previous and concomitant medications will be coded.
Information on coding dictionaries will be provided in a Data Management Plan.

16 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Monitoring

The monitoring visits will be conducted by personnel of the CRO, PAREXEL.

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements, CFDA-GCP and the monitoring plan.

Adequate time and availability for monitoring activities should be ensured by the investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the investigator will assure support to the monitor at all times.

The investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorised individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH-GCP and CFDA-GCP guidelines

16.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System that includes quality controls and audits at different study steps with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP and CFDA-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOAC principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete).

The clinical site(s) is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, CFDA GCP and any applicable regulatory requirement(s).

This protocol has been audited by the Sponsor QA.

The CROs and the sponsor will be responsible for their respective activities.

The sponsor may transfer any or all of the sponsor’s trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

16.3 Applicable SOPs

The sponsor, the clinical centre and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for Sponsor review, if required.

16.4 Data access

The investigator and the CRO(s) will ensure that all source data, medical records, CRFs and all other documentation that is relevant to this study will be made accessible for monitoring activities, audits, IEC review, and regulatory inspections.

16.5 Audits and inspections

The sponsors, independent bodies acting on behalf of the sponsor and the CRO have the right to perform audits according to ICH-GCP and CFDA responsibilities.

The study may also be inspected by regulatory authorities.

The investigator(s) and the CRO(s) agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorised individuals to have access to all the study documentation.

17 ETHICAL CONSIDERATIONS

17.1 Ethics and Good Clinical Practice (GCP)

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.

The approval of the study protocol by the relevant Ethics Committee will be obtained before the start of the study.
Study notification to the Competent Authorities will be performed according to the current local regulations.

The present clinical study will be carried out according to the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), CFDA Reg No. 25 "Good Clinical Practice (GCP) Mar 23, 2016 and the applicable local law requirements.

17.2 Informed consent

Before being enrolled into the clinical study, the subjects must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the EC and regulatory authorities. The document will include all the elements required by law according to the ICH-GCP recommendations.
In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organised
- the type of treatment (information on the IMP(s) and treatment procedures, as applicable)
- any potential negative effects attributable to the study product or treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of a subject insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded.

The investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the investigator and the subject.
A copy of the signed form will be given to the subject.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements. The investigator will allow inspection of the forms by authorised representatives of the sponsor, EC

members and regulatory authorities. He/she will confirm, by signing and dating the forms, that informed consent has been obtained.

17.3 Insurance policy

An insurance cover has been issued in favour of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

17.4 Withdrawal of subjects

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

17.4.1 Primary reason for discontinuation

- **Adverse event**: Any (significant) adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 14.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**: pregnancy is the state or condition of having a developing embryo or foetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

17.4.2 Discontinuation procedures

For any subject discontinuing the study, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory

assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening)

- arrange for alternative medical care of the withdrawn subject, if necessary
- record the subject decision about the use of collected biological samples
- report in the CRF date and time of the last dose administration, and date and primary reason of study discontinuation
- record in the CRF any follow-up, if the subject is withdrawn for an AE

Discontinued subjects will not be replaced.

17.5 Study termination

The study will be considered terminated at the date of the last visit of the last subject or upon completion of any follow-up procedure described in the protocol. The investigator and the sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately.

18 ADMINISTRATIVE PROCEDURES

18.1 Material supplied to the clinical centre

Beside the investigational products, the following study material will be supplied to the clinical centre:

- final version of the study protocol
- access to the eCRF
- copy of the SmPC relative to the investigational products
- informed consent forms
- investigator site file
- laboratory supplies

Moreover, before the start of the study, the investigator(s) will be provided with the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and study staff list form.

18.2 Protocol amendments

In order to obtain interpretable results, neither the investigator nor the sponsor will alter the study conditions agreed upon and set out in this protocol. Amendments should be made by mutual agreement between the investigator and the sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol.

All substantial amendments will be sent to the EC and concerned Competent Authorities, as appropriate. The amendment will be applicable only when it is approved, unless the changes consist of urgent safety measures to protect study subjects.

Non-substantial amendments will be notified according to the current local regulations.

18.3 Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

The investigator must keep source documents for each subject in the study. Information present on the CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including lab tests and ECG tracing, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP, CFDA GCP national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

18.4 Study subjects' recruitment

The CRO and its clinical site have detailed SOPs on the recruitment process.

18.5 Confidentiality and data protection

By signing this protocol, the investigator agrees to keep all the information provided by the sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the sponsor (protocols, CRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the sponsor to the investigator cannot be disclosed to others without direct written authorisation from the sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Subjects data collected in the eCRFs during the study will be documented in an anonymous way. If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the monitor, the sponsor and the investigator will be bound to keep this information confidential.

18.6 Publication policy

The Investigator agrees to inform Zambon in advance about his/her intention to divulge any data, results concerning the Confidential Information and/or the study patient to this Agreement. As a consequence hereof, the Investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon's rights to preserve and protect its

intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the study is conducted.

Furthermore, without any prejudice to the Investigator's right to divulge and save for what stated hereinabove, the Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the study hereto.

19 STUDY RESPONSIBLE PERSONS

19.1 Sponsor

Zambon S.p.A., via Lillo del Duca 10, 20091 Bresso (Milan), Italy
Phone: PPD
Fax: PPD

Protocol Review Committee Chairman
PPD PPD

Medical Expert
PPD PPD

19.2 Institutes performing the study

19.2.1 Clinical centre

"Denomination" Address XXXXXXX, "Zip" "City", China
Phone: +00.nnnnnnnnn
Fax: +00.nnnnnnnnn
Email: "Email"@"Specify".com

Principal investigator
"SpecifyName", MD

19.3 Drug assay

Analytical Facility for PK/drug assay:

United-Power Pharma Tech Co., Ltd. (UP-Pharma)
2F, Tower B, No. 33 Science Park Road,
Changping District, Beijing, P.R.China
ZIP Code: 102206

Analytical facilities and procedures are in compliance with the general principles of GLP regulations.

19.4 Co-ordination, data analysis & reporting

PAREXEL International (IRL) Limited ("**PAREXEL**"), a corporation organized under the laws of Ireland with a registered address at 70 Sir John Rogerson's Quay, Dublin 2, Ireland.

19.5 Project Management and Monitoring

PAREXEL International (IRL) Limited ("**PAREXEL**"), a corporation organized under the laws of Ireland with a registered address at 70 Sir John Rogerson's Quay, Dublin 2, Ireland.

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21 APPENDIX 1

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*

CLINICAL TRIAL PROTOCOL

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

Phase I, single centre, single and multiple-dose, open-label, randomised, parallel-group, pharmacokinetics, safety and tolerability study

Protocol Code: Z7219J03

Date: 18 April 2019

Version: Final 2.0

Zambon SpA
Via Lillo del Duca 10
20091 Bresso - Milan - Italy

APPROVAL PAGE

Clinical Trial Title:	A phase I, pharmacokinetics, safety and tolerability study of single and multiple oral doses of safinamide in Chinese adult healthy volunteers.
Protocol Code	Z7219J03
Date:	18 April 2019
Author:	PPD
Sponsor Name and Address:	Zambon SpA Via Lillo del Duca 10 20091 Bresso, Milan, Italy

As agreed and approved:

_____/_____/_____	_____	_____
Date (dd/Mmm/yyyy)	**Principal Investigator**	**SIGNATURE**

Accepted for the Sponsor

_____/_____/_____	_____	_____
Date (dd/Mmm/yyyy)	**Global Chief Medical Officer and Patient's Access Head**	**SIGNATURE**

1 STUDY SYNOPSIS

Title: A phase I, pharmacokinetics, safety and tolerability study of single and multiple oral doses of safinamide in healthy adult Chinese volunteers

Protocol number: Z7219J03

Clinical phase: Phase I

Study design: Phase I, single centre, single and multiple-dose, open-label, randomised, parallel-group, pharmacokinetics, safety and tolerability study

Planned nr. of centres / countries: 1/China

Investigator and centre: *Principal investigator*: TBD

Investigational products:
Test product 1: Xadago® 50 mg safinamide film-coated tablets, Zambon S.p.A., Italy
Test product 2: Xadago® 100 mg safinamide film-coated tablets, Zambon S.p.A., Italy

Dose regimen:
Subjects will be randomised 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) as follows:
Cohort 1: One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets administered o.d. from day 8 to day 14.
Cohort 2: One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7safinamide 100 mg film-coated tablets administered o.d. from day 8 to day 14.

Study treatment is also summarised in the scheme below:

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

The investigational products will be orally administered in the morning, at 8:00±1h, under fasting conditions, with 240 mL (total volume) of still mineral water. A mouth-and-hand check will be performed immediately after dosing to ensure treatment compliance.

Objective: To evaluate safinamide pharmacokinetic profile, safety and tolerability after single and multiple dose administration to healthy adult Chinese volunteers.

End-points:
Primary end-point:
- To evaluate plasma safinamide pharmacokinetic parameters after single and multiple dose administration of the Test investigational products.

Secondary end-points:
- To collect safety and tolerability data after single and multiple dose administration of the Test investigational products.

Study variables:
Primary variables - Pharmacokinetics: The following safinamide PK parameters will be determined on day 1 (after the first dose), on day 8 (after the first multiple dose) and on day 14 (after the last dose):

After single dose and first multiple dose (day 1 and day 8):
- C_{max}: maximum safinamide plasma concentration
- t_{max}: time to achieve C_{max}
- AUC_{0-t}: area under the concentration-time curve from single dose administration to the last observed concentration time t, calculated with the linear up/log down trapezoidal method
- AUC_{0-24}: area under the concentration-time curve in the tau interval (from single dose administration to 24 h post-dose), calculated with the linear up/log down trapezoidal method

STUDY SYNOPSIS (cont.)

Study variables, continued: **Primary variables - Pharmacokinetics, continued:**

After single dose only (day 1):

- Kel: terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points
- $t_{1/2}$: apparent terminal elimination half-life, calculated, if feasible, as $\ln 2/K_{el}$
- $AUC_{0-\infty}$: area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration
- V_d/F: apparent volume of distribution associated with the terminal slope, calculated, if feasible, as $Dose/(AUC_{0-\infty}*K_{el})$
- Cl/F: apparent total body clearance, calculated, if feasible, as $Dose/AUC_{0-\infty}$
- MRT: Mean residence time calculated, if feasible, as $AUMC_{0-\infty}/AUC_{0-\infty}$, were $AUMC_{0-\infty}$ is area under the moment concentration-time curve extrapolated to infinity

After multiple dose (day 14):

- C_{max_ss}: maximum safinamide plasma concentration at steady-state
- t_{max_ss}: time to achieve $C_{max,ss}$
- C_{min_ss}: trough safinamide plasma concentration at steady-state, measured as concentration at 24h
- $AUCss_{0-t}$: area under the concentration-time curve at steady-state from the last dose administration to the last observed concentration time t, calculated with the linear up/log down trapezoidal method
- $AUCss_{0-24}$: area under the concentration-time curve at steady-state in the tau interval (from the last dose administration to 24 h post dose), calculated with the linear up/log down trapezoidal method
- C_{ave_ss}: average safinamide plasma concentration at steady-state, calculated as AUC_{ss0-24} /tau
- R: accumulation ratio, calculated as AUC_{ss0-24}/ Day 8 AUC_{0-24}
- DF%: peak-trough fluctuation over one dosing interval at steady-state, calculated as $(C_{max,ss} - C_{min,ss})/C_{ave,ss}*100$
- $V_{d,ss}/F$: apparent volume of distribution at steady-state associated with the terminal slope, calculated, if feasible, as $Dose/(AUCss_{0-24}*K_{el})$
- $Cl_{,ss}/F$: apparent total body clearance at steady-state, calculated, if feasible, as $Dose/AUCss_{0-24}$

Secondary variables - Safety and tolerability:

- Treatment emergent adverse events, vital signs (blood pressure, heart rate), body weight, physical examinations, clinical laboratory parameters, ECG.

Analytics: Plasma samples for safinamide determination will be collected 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**);
- pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (**day 8**)
- pre-dose on **days 10, 11, 12, 13**.

Analyses will be performed at a certified bioanalytical laboratory (to be designated). The analytical method will be detailed in the study analytical plan. Analytical facilities and procedures will be in compliance with the general principles of GLP regulations.

Safety evaluation: Safety of the study treatments will be evaluated on the basis of treatment-emergent adverse events, clinical safety laboratory tests, vital signs, ECGs, and physical examinations.
Adverse events will be collected throughout the study. Vital signs will be measured at screening, during the study and at final visit or early termination visit (ETV) in case of discontinuation. Physical examinations, ECGs and clinical laboratory tests will be performed at screening and final visit/ETV.

Sample size: Twelve (12) healthy male and female Chinese volunteers per 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 (1).

Main selection criteria:

Inclusion criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males and females, 18-45 year old inclusive
3. *Ethnicity:* Chinese

STUDY SYNOPSIS (cont.)

Main selection criteria, continued: Inclusion criteria, continued:

4. *Weight:* body weight ≥ 50 kg;
5. *Body Mass Index*: 19-26 kg/m^2 inclusive
6. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting/supine position
7. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. *No nicotine addiction (smoker subjects only)*: ability to abstain for smoking for the duration of the clinical study
9. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception during the study and two weeks post-dose:
   a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
   b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   c. A male sexual partner who agrees to use a male condom with spermicide
   d. A sterile sexual partner

   Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.
   For all women, pregnancy test result must be negative at screening and day -1.

Exclusion criteria:

1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; positive result on HIV, hepatitis B, (HBV) (except for vaccination), hepatitis C (HCV). Retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
6. *Medications*: medications, including over the counter medications, herbal remedies and traditional Chinese remedies for 2 weeks before the start of the study. In particular statins and HMG-CoA reductase inhibitors in the 2 weeks before the screening visit; medicinal products that are BCRP substrates; treatment with morphine or other similar opioids, whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives and antiepileptic drugs in the 4 weeks before the screening visit; treatment with any known enzyme inhibiting or inducing agent within 4 weeks preceding the screening visit. Hormonal contraceptives for women will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study
8. *Blood donation*: blood donations or blood components transfusion for 3 months before this study
9. *Abuse drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes or equivalent amount of tobacco per day within 3 months prior to day -1)
10. *Abuse drug test*: positive result at urine drug test at screening or day-1
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians; consumption of grapefruit or products containing grapefruit within 48 hours prior to the enrolment; consumption of beverages containing xanthines (e.g. coffee, tea, soda, coffee, milk, energy drinks) within 48 hours prior to the enrolment
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

STUDY SYNOPSIS (cont.)

Schedule:
Procedures and assessments during study visits are listed in the table below:

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Subjects' screening number assignment ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications check ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Clinical laboratory analyses: haematology, blood chemistry, urinalysis, serum virology and serum pregnancy test (women) ➢ Urine multi-drug kit test ➢ Adverse events check ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	
Period 1 Cohorts 1 and 2 - Visit 2	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Urine pregnancy test (women) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subjects' randomisation number assignment ➢ Adverse events and concomitant medications check	<u>Day -1</u> Arrival at the clinical centre in the evening. Confinement until the morning of day 3. Standardized dinner Fasting for at least 10 h (overnight)
Period 1 Cohorts 1 and 2 - Visit 3	*Days 1 - 3*	<u>Day 1</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose <u>Day 1 - Day 3</u> ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose ➢ AEs and concomitant medications check	<u>Day 1</u> Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. <u>Day 2</u> Standardized breakfast, lunch and dinner <u>Day 3</u> Standardized breakfast. Discharge from the clinical centre in the morning after the 48-h blood sampling for PK analysis

STUDY SYNOPSIS (cont.)

Study schedule, continued:			
Period 1 Cohorts 1 and 2 - Visit 4	*Days 4 - 5* *Ambulatory visits*	Days 4 - 5 ➢ Blood sample collection for pharmacokinetic analysis at 72 h (day 4) and 96 h (day 5) post-dose ➢ AEs and concomitant medications check Days 5 ➢ Vital signs measurement at 96 h post-dose from Day 1	Days 4 - 5 The subjects will return to the clinical centre each day in the morning for ambulatory blood sampling and safety checks Day 5 Subjects will be reminded to return to the clinical centre in the morning of day 8 for study Period 2.
A wash-out of 7 days will elapse between the single dose administered on day 1 and the first multiple dose administered on day 8			
Period 2 Cohorts 1 and 2 - Visit 5	*Days 8 -9*	Day 8 - Day 9 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ AEs and concomitant medications check Day 8 only ➢ Vital signs measurement at pre-dose and 2 h post-dose	Days 8-9 Subjects will be confined from the morning of day 8 (before investigational product administration) up to the morning of day 9. Day 8 Standardized lunch at approximately 5 h post-dose; Standardized dinner at approximately 13 h post-dose Day 9 Standardized breakfast. Subjects will be discharged in the morning, after the 24-h blood sampling for PK analysis standardized.
Period 2 Cohorts 1 and 2 - Visit 6	*Days 10 - 13* *Ambulatory visits*	Days 10 - 13 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at pre-dose on each day ➢ Vital signs measurement before blood sampling and investigational product administration ➢ AEs and concomitant medications check	Days 10 - 13 The subjects will return to the clinical centre each day in the morning for ambulatory pre-dose blood sampling for PK analysis, investigational product administration and safety checks

STUDY SYNOPSIS (cont.)

Period 2 **Cohorts 1 and 2 - Visit 7**	*Days 14 - 17*	Day 14 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose Day 14 - Day 17 ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose ➢ AEs and concomitant medications check	Day 14 Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose Days 15-16 Standardized breakfast, lunch and dinner. Day 17 Standardized breakfast. Discharge from the clinical centre in the morning after the 72-h blood sampling for PK analysis
Period 2 **Cohorts 1 and 2 - Visit 8**	*Day 18* *Ambulatory visit*	Day 18 ➢ Blood sample collection for pharmacokinetic analysis at 96 h post-dose ➢ Vital signs measurement at 96 h post-dose from Day 14 ➢ AEs and concomitant medications check Final visit assessments (see below) and discharge	Day 18 The subjects will return to the clinical centre in the morning for ambulatory blood sampling and safety checks Subjects will be discharged after final visit assessments (see Final visit/ETV below)
Final Visit/ETV	*Day 18. At ETV in case of early termination*	The following final assessments will be performed after the 96-h time-point assessments (day 18) or at ETV in case of early discontinuation: ➢ Physical examination (body weight, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ Urine pregnancy test (women) Vital signs assessments performed at 96 h post-dose on day 18 will be considered as the final assessment. Vital signs will also be measured at ETV, in case of early discontinuation. AEs and concomitant medications will also be checked at final visit/ETV. AEs will be captured up to the end of study visit. In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

STUDY SYNOPSIS (cont.)

Life style and constraints:
During the study, the subjects will be confined as follows:
- *from the evening preceding the first administration (study day -1) until the morning of day 3.*
- *from the morning of day 8 to the morning of day 9.*
- *from the morning of day 14 to the morning of day 17.*

Subjects will be discharged from the study after final assessments, as specified above (Final visit/ETV).
The subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before investigational product administration. On days 1, 8 and 14, subjects will remain fasted up to 5 h post-dose. Standardized meals will be served at the clinical centre according to the schedule above. Water will be allowed as desired, except for one hour before and one hour after investigational product administration. Coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement starting 48 h before the first administration until the end of the study. Smoking is not allowed for the whole study duration. Routine ambulant daily activities will be strongly recommended. Hazardous, strenuous or athletic activities will not be permitted.

Data analysis:
The data documented in this trial and the clinical parameters measured will be analysed using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.
Analysis set:
Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics
Safety set: all r**andomised** subjects who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for the safety analyses.

PK set: all randomised subjects who fulfil the study protocol requirements in terms of investigational medicinal products intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the PK analysis.

Safety Assessments:
The statistical analysis of demographic and safety data will be performed using SAS®.
The safety and tolerability of the investigational products will be evaluated on the basis of treatment-emergent adverse events occurrence, laboratory tests and other safety assessments (see section above).
All adverse events, adverse drug reactions (ADR) and serious adverse events (SAEs), if applicable, will be coded using the Medical Dictionary for regulatory Activities and summarized by system organ class and preferred term, incidence, severity and relationship to study drug.
Pharmacokinetics:
The pharmacokinetic parameters will be calculated with a Non-Compartmental Analysis (NCA) using Phoenix WinNonlin v6.3 (or higher). Pharmacokinetic data will be listed and summarised by descriptive statistics.

Study duration:
Maximum study duration for both cohort 1 and 2 will be 32 days including screening period, study Period 1, washout and study Period 2.

2 STUDY SCHEDULE (A MORE DETAILED TABLE IS SHOWN IN APPENDIX 1)

ACTIVITIES		Period 1			Period 2				Final visit/ETV[1]
	Screening	Single Dose			Multiple Dose				
Visit	V1	V2	V3	V4	V5	V6	V7	V8	
Day	Day -14/-2	Day -1	Day 1/3	Day 4/5	Day 8/9	Day 10/13	Day 14/17	Day 18	Day 18[2]
Informed consent	x								
Demography	x								
Lifestyle	x								
Medical and surgical history	x								
Physical examination[3]	x								x
Prior and concomitant medications	x	x	x	x	x	x	x	x	x
Height	x								
Body Weight[3]	x								x
Laboratory analysis[4]	x								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)	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		x							
Urine pregnancy test (women)		x							x
ECG[6]	x								x
Inclusion/exclusion criteria	x	x							
Subject eligibility	x	x							
Enrolment and randomisation		x							
Confinement		x	x		x		x		
Discharge			x (Day 3)		x (Day 9)		x (Day 17)		
Ambulatory visits				x		x		x	
Investigational product administration			x[7] (Day 1)		x[7]	x[7]	x[7] (Day 14)		
Blood sampling for PK analysis			x[8]	x[8]	x[9]	x[10]	x[8]	x[8]	
Standardized meals[11]		x	x		x		x		
Adverse event monitoring[12]	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 after 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: standardized 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*

3 TABLE OF CONTENTS

TABLES

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LIST OF ABBREVIATIONS

β-HCG	human chorionic gonadotropin β
γ-GT	γ-Glutamyl transpeptidase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOAC	Attributable-Legible-Contemporaneous-Original-Accurate-Complete
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from time zero to time t
$AUCss_{0-t}$ or $AUC_{0-t,ss}$	Area under the concentration-time curve at steady state
$AUC_{0-\infty}$	Area under the concentration vs. time curve up to infinity
AUC_{0-24h}	Area under the concentration-time curve in the tau interval
$AUCss_{0-24}$ or $AUC_{0-24h,ss}$	Area under the concentration-time curve at steady state in the tau interval
BUN	Blood Urea Nitrogen
BCRP	Breast Cancer Resistance Protein
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cl/F	Apparent total body clearance
$C_{ave\ ss}$	Average drug concentration at steady state
C_{max}	Maximum drug concentration
C_{max_ss}	Maximum drug concentration at steady state
$C_{mix\ ss}$	Trough drug concentration at steady state
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically Significant
CV	Coefficient of Variation
DF%	Peak-trough fluctuation over one dosing interval at steady-state
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IUD	Intra-Uterine Device
K_{el}	Terminal elimination rate constant
LLOQ	Lower Limit of Quantification
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit
MAO	Monoamino oxidase
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration

MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MW	Molecular Weight
N	Normal
NA	Not Applicable
NC	Not calculated
NCS	Not clinically significant
OTC	Over The Counter
PD	Parkinson's disease
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R_{acc}	Accumulation ratio
RBC	Red Blood Cells
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SNRI	Serotonin–norepinephrine reuptake inhibitors
SOC	System Organ Class
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test
T1	Xadago® 50 mg
T2	Xadago® 50 mg
TEAE	Treatment-Emergent Adverse Event
THC	Delta-9-tetrahydrocannabinol
$t_{1/2}$	Apparent terminal elimination half-life
t_{max}	Time to achieve C_{max}
V_d/F	Apparent volume of distribution associated with the terminal slope
WBC	White Blood Cells
WHODDE	World Health Organisation Drug Dictionary Enhanced

4 INTRODUCTION

4.1 Safinamide

4.1.1 Background

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 authorisation 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).

Safinamide uniquely combines potent, selective and reversible inhibition of monoamino oxidase B (MAO-B) with blockade of voltage-dependant Na^+ and Ca^{2+} channels and inhibition of glutamate release (4,8), thus showing a novel mode of action, targeting both dopaminergic and glutaminergic systems (9,10).
Data from Phase III clinical studies gave evidence that safinamide 50 or 100 mg/day improves the motor function in Parkinson's disease when prescribed as add-on therapy to dopamine agonists or L-dopa (3).

4.1.2 Clinical pharmacology and pharmacokinetics

Safinamide pharmacokinetics after single and multiple dose administrations have been described (11,12). At single ascending oral doses ranging from 2.5 to 10.0 mg/kg, safinamide was absorbed in a linear and dose-proportional fashion. Peak plasma levels were obtained on average at 1.8 to 2.8 h post-dose. Concentrations declined with a terminal half-life of 20 - 23h (11,12). Absolute bioavailability is high (95%), showing that safinamide is almost completely absorbed after oral administration and first pass metabolism is negligible (SmPC, 3). A complete long-lasting inhibition of platelet MAO-B activity was observed at all doses tested. Food intake prolonged the rate but did not affect the extent of safinamide absorption (11,12).
Studies in healthy volunteers (13,15) demonstrated that safinamide does not affect oral tyramine metabolism mostly mediated by the intestinal MAO-A, and confirm that it can be administered without tyramine-related dietary restrictions.

4.1.3 Safety

The overall safety profile of Xadago® is based on the clinical development program performed on over 3000 subjects, of which over 600 were treated for more than 2 years.

The most common side effects related to safinamide are dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension. Serious adverse reactions, such as hypertensive crisis (high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, CPK increase), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension, are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors.

With MAO-inhibitors there have been reports of drug interactions with concomitant use of sympathomimetic medicinal products. Impulse control disorders, pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments.

A complete list of adverse reactions observed with safinamide is presented in the SmPC (3).

4.2 Study rationale

The present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations (1).

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.

4.3 Risks and benefits

For AEs occurred with safinamide in previous clinical studies, please refer to § 4.1.3 and the SmPC (3). The most common side effects are dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension.

Based on the clinical experience, no particular risks are expected for the study subjects considering safinamide 50 mg and 100 mg multiple dose administrations.

5 STUDY OBJECTIVES

The objective of the study is to evaluate safinamide pharmacokinetic profile, safety and tolerability after single and multiple dose administration to healthy adult Chinese volunteers

5.1 Primary end-point

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

5.2 Secondary end-point

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

6 CLINICAL SUPPLIES

6.1 Treatment

6.1.1 Description of investigational products

TEST PRODUCT 1 (T1)	
Name	Xadago® 50 mg film-coated tablets
Active ingredient	Safinamide methanesulphonate (corresponding to 50 mg safinamide)
Marketing Authorization Holder	Zambon S.p.A., Italy
Pharmaceutical form	Film-coated tablets
Dose	Single 50 mg dose on day 1 Multiple 50 mg doses, once daily, for 7 days
Administration route	Oral

TEST PRODUCT 2 (T2)	
Name	Xadago® 100 mg film-coated tablets
Active ingredient	Safinamide methanesulphonate (corresponding to 100 mg safinamide)
Marketing Authorization Holder	Zambon S.p.A., Italy
Pharmaceutical form	Film-coated tablets
Dose	Single 100 mg dose on day 1 Multiple 100 mg doses, once daily, for 7 days
Administration route	Oral

6.1.2 Dose regimen

Subjects will be randomised 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 randomised, parallel-group design, as follows:

- Cohort 1: One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets administered o.d. from day 8 to day 14.

- Cohort 2: One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 100 mg film-coated tablets administered o.d. from day 8 to day 14.

Dose regimens are also summarised in the scheme below:

Table 6.1.2.1 Study dose regimen

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

6.1.3 Route and method of administration

The investigational products will be orally administered in the morning, at 8:00±1h, under fasting conditions, with 240 mL (total volume) of still mineral water.

A mouth-and-hand check will be performed immediately after dosing to ensure treatment compliance.

6.1.4 Investigational product distribution

All doses of the investigational products will be administered at the clinical centre by the investigator or by his/her deputy. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

6.2 Packaging and labelling

Packaging and labelling for the clinical study will be performed by a GMP compliant vendor, delegated by Zambon S.p.A., Italy.

Subjects' kit labelling will report all the information according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4, 16), as follows:

a. Name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical study)

b. Pharmaceutical dosage form, route of administration, quantity of dosage units, and the name/identifier and strength/potency

c. The batch and/or code number to identify the contents and packaging operation

d. A study reference code allowing identification of the study, site, investigator and sponsor if not given elsewhere

e. A blank space for subject enrolment Nr. (to be reported by hand by the Investigator) and where relevant, the visit number

f. The name of the investigator (if not included in (a) or (d))

g. Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)

h. “For clinical study use only” or similar wording

i. The storage conditions

j. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity

k. "Keep out of reach of children"

The label will be in Chinese language.

6.3 Storage conditions

The investigational products will be stored at ≤ 25° C in a dry locked place, sheltered from light.

6.4 Drug accountability

The vendor delegated by Zambon S.p.A., Italy, will provide the clinical centre with a sufficient number of individual subject kits to conduct the study, plus sufficient reserve kits.

After receipt of the drug supply, the Pharmacist will confirm in writing by signing and dating standard drug accountability forms. At the end of the study, the drug product will be maintained in the original containers.

At the end of the study, used, unused and partially used supplies of the investigational products, provided by the vendor delegated by Zambon S.p.A., Italy, will be stored as detailed in § 6.3 above and then disposed of (upon sponsor written authorisation), after assessment of drug accountability.

7 INVESTIGATIONAL PLAN

7.1 Overall study design

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

7.2 Discussion of design

Following a specific request of CFDA, the present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations (1).

Safinamide has recently been granted marketing authorization in EU, Norway and Switzerland on the basis of the results of clinical trials performed in European countries. 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.

Two single doses (i.e. 50 and 100 mg) of safinamide will be administered to two subject' cohorts. The study will continue with multiple administrations of safinamide 50 and 100 mg, orally taken once a day for 7 days.

The 50 and 100 mg oral doses have been selected according to the common clinical practice (see Xadago® SmPC). These doses were investigated in the previously performed Phase III clinical trials. The volunteers will be assigned to the two cohorts according to the study randomised, parallel-group design.

Safinamide pharmacokinetic profile will be investigated after single dose, according to CFDA guidance requirements, and at steady state since multiple doses are administered in the clinical practice. Safinamide steady state should be reached after 5 or 6 days of treatment (day 13-14 in this study). Safinamide pre-dose concentrations will be assessed before the last 5 doses (days 10-14).

An open design was chosen. However, no bias on study outcome is expected considering that the study PK endpoints are based on the objective measurement of safinamide in plasma.
Blood sampling time-points were selected on the basis of the known PK profile of safinamide. The sampling time lasts for about 4-7 elimination half-lives (mean PK half-life: 20-23 h) after both single dose and the last multiple dose administration.

8 STUDY POPULATION

8.1 Target population

Twenty-four (24) healthy male and female Chinese volunteers, aged 18-45 years inclusive, will be enrolled into the study.

8.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all these criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males and females, 18-45-year old inclusive
3. *Ethnicity:* Chinese
4. *Weight:* body weight ≥ 50 kg;
5. *Body Mass Index*: 19-26 kg/m^2 inclusive
6. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting/supine position
7. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. *No nicotine addiction (smoker subjects only)*: ability to abstain for smoking for the duration of the clinical study
9. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception during the study and two weeks post-dose:
    a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
    b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
    c. A male sexual partner who agrees to use a male condom with spermicide
    d. A sterile sexual partner

    Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.
    For all women, pregnancy test result must be negative at screening and day -1.

8.3 Exclusion criteria

Subjects meeting any of these criteria will not be enrolled in the study:

1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study

3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; positive result on HIV, hepatitis B (HBV) (except for vaccination), hepatitis C (HCV). Retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
6. *Medications*: medications, including over the counter medications, herbal remedies and traditional Chinese remedies for 2 weeks before the start of the study. In particular statins and HMG-CoA reductase inhibitors in the 2 weeks before the screening visit; medicinal products that are BCRP substrates; treatment with morphine or other similar opioids, whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives and antiepileptic drugs in the 4 weeks before the screening visit; treatment with any known enzyme inhibiting or inducing agent within 4 weeks preceding the screening visit. Hormonal contraceptives for women will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study
8. *Blood donation*: blood donations or blood components transfusion for 3 months before this study
9. *Abuse drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes or equivalent amount of tobacco per day within 3 months prior to day-1)
10. *Abuse drug test*: positive result at urine drug test at screening or day-1
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians; consumption of grapefruit or products containing grapefruit within 48 hours prior to the enrolment; consumption of beverages containing xanthines (e.g. coffee, tea, soda, coffee, milk, energy drinks) within 48 hours prior to the enrolment
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

8.3.1 Not allowed treatments

No medication, including OTC, herbal remedies and traditional Chinese remedies, will be allowed for 2 weeks before the start of the study and during the whole study duration.

Statins and HMG-CoA reductase inhibitors use will not be allowed for 2 weeks before and during the study. Wash-out interval for the treatment with morphine or other similar opioids,

whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives, antiepileptic drugs and the treatment with any known enzyme inhibiting or inducing agent or any investigational drugs intake will be at least 4 weeks before the screening visit. Hormonal contraceptives are allowed.

Paracetamol will be allowed as therapeutic counter-measure for adverse events (AEs) according to the investigator’s opinion. The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the investigator, together with the sponsor, considers it could affect the study assessments or outcome.

9 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

9.1 Study visits and procedures

Each study subject completing the study will undergo 8 visits plus a final visit.

The study protocol foresees 2 periods: in the first one the investigational products are administered in single dose, in the second one in multiple doses. The single dose in the first period and the first dose in the second period are separated by a wash-out interval of 7 days. Maximum and minimum study duration will be 32 and 20 days, respectively, screening visit included.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical centre by the 1st screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the clinical centre (or a telephonic follow-up, if applicable) by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – visit 1: between day -14 and day -2
  - Period 1 – visit 2: day -1

- **Interventional phase**
  - Period 1 – visit 3: days 1-3: single dose and blood sampling for PK analysis
  - Period 1 – visit 4: days 4-5: ambulatory visits - blood sampling for PK analysis
  - Wash-out interval of 7 days
  - Period 2 – visit 5: days 8-9: first multiple dose and blood sampling for PK analysis
  - Period 2 – visit 6: days 10-13: ambulatory visits - multiple doses and blood sampling for PK analysis
  - Period 2 - visit 7: days 14-17: last multiple dose and blood sampling for PK analysis
  - Period 2 - visit 8: day 18: blood sampling for PK analysis

- **Final phase**
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)

Study schedule

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Subjects' screening number assignment ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications check ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Clinical laboratory analyses: haematology, blood chemistry, urinalysis, serum virology and serum pregnancy test (women) ➢ Urine multi-drug kit test ➢ Adverse events check ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	
Period 1 Cohorts 1 and 2 - Visit 2	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Urine pregnancy test (women) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subjects' randomisation number assignment ➢ Adverse events and concomitant medications check	<u>Day -1</u> Arrival at the clinical centre in the evening Confinement until the morning of day 3. Standardized dinner Fasting for at least 10 h (overnight)
Period 1 Cohorts 1 and 2 - Visit 3	*Days 1 - 3*	<u>Day 1</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose <u>Day 1 - Day 3</u> ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose ➢ AEs and concomitant medications check	<u>Day 1</u> Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose <u>Day 2</u> Standardized breakfast, lunch and dinner <u>Day 3</u> Standardized breakfast. Discharge from the clinical centre in the morning after the 48-h blood sampling for PK analysis

Study schedule, continued

Period 1 **Cohorts 1 and 2 - Visit 4**	*Days 4 - 5* *Ambulatory visits*	Days 4 - 5 ➢ Blood sample collection for pharmacokinetic analysis at 72 h (day 4) and 96 h (day 5) post-dose ➢ AEs and concomitant medications check Days 5 ➢ Vital signs measurement at 96 h post-dose from Day 1	Days 4 - 5 The subjects will return to the clinical centre each day in the morning for ambulatory blood sampling and safety checks Day 5 Subjects will be reminded to return to the clinical centre in the morning of day 8 for study Period 2.
A wash-out of at least 7 days will elapse between the single dose administered on day 1 and the first multiple dose administered on day 8			
Period 2 **Cohorts 1 and 2 - Visit 5**	*Days 8 -9*	Day 8 - Day 9 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ AEs and concomitant medications check Day 8 only ➢ Vital signs measurement at pre-dose and 2 h post-dose	Days 8-9 Subjects will be confined from the morning of day 8 (before investigational product administration) up to the morning of day 9. Day 8 Standardized lunch at approximately 5 h post-dose; Standardized dinner at approximately 13 h post-dose Day 9 Standardized breakfast. Subjects will be discharged in the morning, after the 24-h blood sampling for PK analysis
Period 2 **Cohorts 1 and 2 - Visit 6**	*Days 10 - 13* *Ambulatory visits*	Days 10 - 13 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at pre-dose on each day ➢ Vital signs measurement before blood sampling and investigational product administration ➢ AEs and concomitant medications check	Days 10 - 13 The subjects will return to the clinical centre each day in the morning for ambulatory pre-dose blood sampling for PK analysis, investigational product administration and safety checks

Study schedule, continued

Period 2 **Cohorts 1 and 2 - Visit 7**	*Days 14 - 17*	<u>Day 14</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose and 2 h post-dose <u>Day 14 - Day 17</u> ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose ➢ AEs and concomitant medications check	<u>Day 14</u> Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose <u>Days 15-16</u> Standardized breakfast, lunch and dinner. <u>Day 17</u> Standardized breakfast. Discharge from the clinical centre in the morning after the 72-h blood sampling for PK analysis
Period 2 **Cohorts 1 and 2 - Visit 8**	*Day 18* *Ambulatory visit*	<u>Day 18</u> ➢ Blood sample collection for pharmacokinetic analysis at 96 h post-dose ➢ Vital signs measurement at 96 h post-dose from Day 14 ➢ AEs and concomitant medications check Final visit assessments (see below) and discharge	<u>Day 18</u> The subjects will return to the clinical centre in the morning for ambulatory blood sampling and safety checks. Subjects will be discharged after final visit assessments (see Final visit/ETV below)
Final Visit/ETV	*Day 18. At ETV in case of early termination*	The following final assessments will be performed after the 96-h time-point assessments (day 18) or at ETV in case of early discontinuation: ➢ Physical examination (body weight, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ Urine pregnancy test (women) Vital signs assessments performed at 96 h post-dose on day 18 will be considered as the final assessment. Vital signs will also be measured at ETV, in case of early discontinuation. AEs and concomitant medications will also be checked at final visit/ETV. AEs will be captured up to the end of study visit. In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

9.2 Diet, lifestyle and study restrictions

During the study, the subjects will be confined at the clinical centre as follows:

Period 1:
- from the evening preceding the first administration (study day -1) until the morning of day 3.

Period 2:
- from the morning of day 8 to the morning of day 9.
- from the morning of day 14 to the morning of day 17.

Subjects will be discharged from the study after final assessments (Final visit or ETV).

The subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before investigational product administration. On days 1, 8 and 14, subjects will remain under fasting conditions up to 5 h post-dose.
Standardized meals will be served at the clinical centre according to the schedule below:

- Day -1: standardized 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 Days 17: standardized breakfast

Water will be allowed as desired, except for 1 h before and 1 h after investigational product administration. Coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement starting 48 h before the first administration until the end of the study. Smoking is not allowed for the whole study duration.

Routine ambulant daily activities will be strongly recommended. Hazardous, strenuous or athletic activities will not be permitted.

10 DESCRIPTION OF SPECIFIC PROCEDURES

10.1 Physical examination

Full physical examinations will be performed at screening and final visit/ETV. Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs.
All clinically significant abnormalities after the screening visit will be recorded as AEs.

10.1.1 Body weight

Body weight will be recorded at screening and final visit/ETV.
Subjects will be weighed (kg) lightly clothed without shoes. Height will be measured at screening only and Body Mass Index (BMI) will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

10.1.2 Vital signs

Subjects' blood pressure and heart rate will be measured by the investigator or his deputy after 5 min at rest (sitting/supine position) at the following times:

- at screening
- on day 1, day 8 and day 14: at pre-dose and 2 h post-dose
- on day 5 and day 18: at 96 h post-dose
- on days 10-13: at pre-dose
- at ETV (if applicable).

10.1.3 ECGs

12-Leads ECGs will be performed (supine position) at screening and final visit/ETV.

Date/time of the ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. Hard copies of the ECGs will be attached as source document at site.

10.2 Clinical laboratory assays

Samples of blood and urine will be collected. The following laboratory analyses will be performed at the screening visit:

HAEMATOLOGY
Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, haemoglobin (conv. units), haematocrit, MCV, MCH, MCHC, thrombocytes.

BLOOD CHEMISTRY
Electrolytes: sodium, potassium, calcium, chloride, inorganic phosphorus
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: total bilirubin, creatinine, glucose, urea or BUN, uric acid, total cholesterol, triglycerides
Proteins: total proteins

Serum pregnancy test (women).

URINE ANALYSIS
Urinalysis: pH, specific gravity, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, leukocytes, erythrocytes, flat cells, crystals, cylinders.

SERUM VIROLOGY
Hepatitis B (HBs antigen), **Hepatitis C** (HCV antibodies), **HIV 1/2** (HIV Ag/Ab combo).

A urine drug test will be performed at the clinical centre at screening, using a urine multi-drug kit. The following drugs will be assessed: cocaine, amphetamine, morphine, cannabis, benzodiazepines, barbital.

A serum pregnancy test will be performed by the laboratory at screening, as listed above. Urine pregnancy test will be performed on day -1 of each study period at the clinical centre and at the final visit/ETV.

The same analyses, with the exception of urine drug test and virology, will be performed at the final visit/ETV.

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be reported in the individual eCRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs.

10.3 Sampling for pharmacokinetic analysis

10.3.1 Venous blood sampling

Venous blood samples (up to 10 mL) will be collected from a forearm vein at the following times:

- At pre-dose (0 h), 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 (days 1-5) and the last multiple dose (days 14-18)
- At pre-dose on days 10-13
- At pre-dose (0 h) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (days 8-9)

Actual sampling times for each subject will be recorded in the individual CRFs. The actual sampling times should not exceed the recommended tolerance ranges presented in the following table. Any deviation outside the recommended ranges will be verified through Data

Clarification Forms and, if confirmed, will be reported as protocol deviation, although it will not automatically lead to the exclusion of the concerned subjects from the PK set.

Table 10.3.1.1 Tolerance ranges for the scheduled sampling times

Sampling time	Tolerance range
Pre-dose (0)	Within 30 minutes before investigational product administration
0.5 h (30 min)	± 1 min
1, 1.5 h	± 3 min
2, 3, 4 h	± 5 min
6, 8, 12, 16, 24, 36, 48, 72, 96 h	± 10 min

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20 I.U./mL Na-heparin. The first 2 mL of blood will be discarded at each collection time to avoid contamination of the sample with heparin.

The remaining 8 mL will be collected from the catheter and transferred with a syringe into heparinised tubes (Li-heparin).
Samples handling and processing is described in study specific lab manual.

10.3.2 Analytics

The concentration of safinamide in plasma samples will be determined at a certified analytical laboratory (to be designated). Analyses will be performed according to the general Principles of "OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and GCP.

The method validation report and the analytical report will be attached to the final report.

10.3.3 Labelling, storage and transport of samples

10.3.3.1 Samples labelling

Labels and labelling process are described in the study specific lab manual.

10.3.3.2 Samples storage and transport

During the study the samples will be stored at ≤- 70° C. At the end of each collection day, aliquots 1 and 2 will be stored in separate freezers.

All aliquots 1, packed in sufficient dry ice, will be shipped by an authorised courier from the clinical centre (China) to the analytical laboratory.

11 ASSIGNMENT OF STUDY TREATMENT

11.1 Randomisation

Randomisation will be used to minimize bias in the assignment of subjects to treatment cohorts, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) will be evenly balanced across treatment cohorts.
The randomisation schedule will be computer-generated by the CRO biostatistician using SAS®.
The randomisation schedule will be attached to the final clinical study report.

11.2 Treatment allocation

Subjects will be randomised 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 randomised, parallel-group design.

On day -1, Period 1, subjects will be assigned a randomisation number, which will be used to assign the study treatment according to the randomisation schedule, as detailed above.
Subjects who prematurely discontinue participation after randomisation will not be replaced.

11.3 Blinding

This is an open study. No masking procedure will be applied.
The open label design is considered appropriate for the primary objective of pharmacokinetic characterization, because PK properties and assessments are not prone to bias of observation by the investigators or the subjects.

12 EVALUATION PARAMETERS

12.1 Study variables

12.1.1 Primary variables

The following safinamide PK parameters will be determined on day 1 (after the first dose), on day 8 (after the first multiple dose) and on day 14 (after the last dose):

After single dose and first multiple dose (day 1 and day 8)

- C_{max}, t_{max}, AUC_{0-t}, and AUC_{0-24h}

After single dose only (day 1):

- K_{el}, $t_{1/2}$, $AUC_{0-\infty}$, V_d/F, Cl/F and MRT

After multiple dose (day 14):

- C_{max_ss}, t_{max_ss}, C_{min_ss}, $AUC_{0-t,ss}$, $AUC_{0-24h,ss}$, C_{ave_ss}, R_{acc}, DF%, $Vd_{,ss}/F$ and $Cl_{,ss}/F$

12.1.2 Secondary variables

- Treatment emergent adverse events (TEAEs), vital signs (blood pressure, heart rate), body weight, physical examinations, clinical laboratory parameters, ECG.

12.2 Pharmacokinetic assessments

12.2.1 Pharmacokinetic parameters

The following safinamide PK parameters will be measured and/or calculated with a Non-Compartmental Analysis (NCA) using Phoenix WinNonlin v6.3 (or higher).

After single dose and first multiple dose (day 1 and day 8):

C_{max}:	Maximum safinamide plasma concentration
t_{max}:	Time to achieve C_{max}
AUC_{0-t}:	Area under the concentration-time curve from single dose administration to the last quantifiable concentration time t
AUC_{0-24h}:	Area under the concentration-time curve in the tau interval (from single dose administration to 24 h post dose)

After single dose (day 1):

K_{el}:	Apparent terminal elimination rate constant, calculated, if feasible, from the slope of a log-linear regression using at least 3 last concentration > LLOQ points
$t_{1/2}$:	Apparent terminal elimination half-life, calculated, if feasible, as $\ln 2/K_{el}$
$AUC_{0-\infty}$:	Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable drug concentration
V_d/F:	Apparent volume of distribution associated with the terminal slope, calculated, if feasible, as $Dose/(AUC_{0-\infty}*K_{el})$

Cl/F: Apparent total body clearance, calculated, if feasible, as Dose/$AUC_{0-\infty}$

MRT: Mean residence time, calculated, if feasible, as $AUMC_{0-\infty}/AUC_{0-\infty}$, were $AUMC_{0-\infty}$ is area under the moment concentration-time curve extrapolated to infinity

The sampling schedule is considered adequate if the ratio $AUC_{0-t}/AUC_{0-\infty}$ equals or exceeds a factor of 0.8 (i.e. if $\%AUC_{extra}$ is <20%) for more than 80% of the individual PK profiles. This assures that AUC_{0-t} covers a sufficient percentage of the theoretical total extent of exposure.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a determination coefficient $R^2 \geq 0.8$. Individual extrapolated parameters, when considered unreliable, will be reported as NC (not calculated).

After multiple dose (day 14):

C_{max_ss}: Maximum safinamide plasma concentration at steady state

t_{max_ss}: Time to achieve C_{max-ss}

AUC_{0-t},ss: Area under the concentration-time curve at steady state from the last dose administration to the last quantifiable concentration time t

$AUC_{0-24h,}$ss: Area under the concentration-time curve at steady state in the tau interval (from the last dose administration to 24 h post dose)

C_{ave_ss}: Average safinamide plasma concentration at steady state, calculated as $AUC_{0-24h,}$ss /tau (24 h)

R_{acc}: Accumulation ratio, calculated as $AUC_{0-24h,ss}/ AUC_{0-24h}$

DF%: Peak-trough fluctuation over one dosing interval at steady-state, calculated as $(C_{max,ss} - C_{min,ss})/C_{ave,ss}*100$

$V_{d,}/F_{ss}$ apparent volume of distribution at steady-state associated with the terminal slope, calculated, if feasible, as Dose/($AUC_{0-24h,}$ss*K_{el})

$Cl_{,}/F_{ss}$ apparent total body clearance at steady-state, calculated, if feasible, as Dose/ $AUC_{0-24h,}$ss

12.3 Safety assessments

Safety and general tolerability of the investigational products will be based on TEAEs, physical examinations, including body weight, vital signs, ECGs and routine haematology, blood chemistry and urinalysis laboratory tests.

13 STATISTICAL METHODS

The data documented in this study and the parameters measured will be evaluated using classic descriptive statistics, i.e. geometric mean, geometric CV (%) (PK data only), arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using Statistical Analysis Software (SAS®) Version 9.3 or higher.
The pharmacokinetic parameters will be calculated using the actual recoded sampling times and non-compartmental methods with Phoenix WinNonlin (Version 6.3 or higher).

13.1 Analysis Sets

13.1.1 Definitions

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 enrolment will be performed through randomised allocation to a treatment cohort. An eligible but not enrolled subject will be defined as a reserve.
A subject will be defined as randomised in the study when he/she is assigned to a randomised treatment cohort.

The following analysis sets will be considered:

- Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics.
- Safety set: all randomised subjects who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for the safety analyses.
- PK set: all randomised subjects who fulfil the study protocol requirements in terms of investigational medicinal products intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the PK analysis.

Each subject will be coded as valid or not valid for the Randomised set, Safety set and PK set. Subjects will be evaluated according to the treatment they actually receive.

13.1.2 Reasons for exclusion from the PK set

Reasons for the exclusion of subjects from the PK set are the following:

Before bioanalysis

- vomiting and diarrhoea 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

If one of these events occurs, it will be noted in the CRF as the study is being conducted.

After bioanalysis

Exclusion of subjects on the basis of pharmacokinetic reasons is possible only for:

- subjects 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 $AUC_{0-\infty}$.
Any data excluded will be discussed in the CSR.

13.2 Sample size and power considerations

Twelve (12) healthy male and female Chinese volunteers / 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 (1).

13.3 Demographic, baseline and background characteristics

Demographic and background characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarised in contingency tables. Quantitative data will be summarised using classic descriptive statistics. The baseline will be the last pre-dose measurement.

13.4 Analysis of pharmacokinetic parameters

A descriptive PK will be presented. The results will be displayed and summarised in tables and figures. Individual and mean curves (+SD at nominal times), indicating inter-subject variability, will be plotted. Data below the lower limit of quantification (BLQ) will be

considered as 0 in the calculations and presented as BLQ in listings and tables. As a consequence of BLQ (i.e. 0) values, calculated geometric means (if requested) could be null. For this reason, in the presence of any null value, the geometric mean will be reported as not calculated (NC).

13.5 Safety and tolerability evaluation

13.5.1 Adverse events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).
AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of investigational product and not worsening after the first dose of investigational product.
- TEAEs: all AEs occurring or worsening after the first dose of investigational product

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship with investigational product and severity.

13.5.2 Physical examination

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed.

13.5.3 Laboratory data

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be listed. All laboratory results will be listed and a table of all the abnormal values will be presented.

13.5.4 Vital signs

Vital signs values will be listed and summarised by descriptive statistics.

13.5.5 Body weight

Body weight values will be listed and summarised by descriptive statistics.

13.5.6 ECG

Date/time of ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. Hard copies of the ECGs will be attached as source document at site.

14 DEFINITION AND HANDLING OF AEs AND SAEs

14.1 Applicable SOPs

AEs definition, classification and management will follow the CRO's SOPs, based upon applicable local and international regulations. The full SOPs or an operative summary will be made available in the CRO.

A brief summary of AE definition, classification and management is reported below.

14.2 Definition of Adverse Event (AE)

An Adverse Event is "*any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*".

AEs include:

- worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- patient/subject deterioration due to the primary illness
- intercurrent illnesses
- drug interactions
- events related or possibly related to concomitant medications
- abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

14.3 Definition of Adverse Drug Reaction (ADR)

An Adverse Reaction is "*any untoward and unintended response to an investigational medicinal product related to any dose administered*".
All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or matter to suggest a causal relationship.

- **Unexpected Adverse Drug Reaction**

An unexpected ADR is: "*An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (Reference Safety Information [RSI]).*

- **Reference Safety Information (RSI)**: in order to assess whether an adverse reaction is expected, the SmPC will be used.

14.4 Definition of Serious Adverse Events or Serious Adverse Drug Reaction

A Serious Adverse Event (SAE) is: "*any untoward medical occurrence or effect that at any dose*:

- results in death
- is life-threatening (i.e. the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but, according to appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

A **Serious Adverse Drug Reaction (SADR)** is an ADR that meets also the definition of SAE.

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is an ADR that is both unexpected (not consistent with the applicable product information, e.g. SmPC) and also meets the definition of a SAE.

A non-serious adverse event is any adverse event that does not meet the criteria listed above for a serious adverse event.

14.5 Definition of Severity of Adverse Events

The term "severe" is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the subject may experience slight discomfort.
- Moderate: causing some limitation of usual activities; the subject may experience annoying discomfort.
- Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

14.6 Definition of Adverse Event causality

Causality shall be determined according to the definition of ADR given in 14.3.

All AE judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor.

The following binary decision for causality will be used:

- Reasonable possibility that the IMP caused the event
- No reasonable possibility that the IMP caused the event

Features supportive of an association include:

- temporal plausibility
- pharmacological properties of the drug or of the substance class
- course of the adverse event after dechallenge and, if applicable, after rechallenge
- specific tests indicating involvement of the drug in the occurrence/worsening of the adverse event
- alternative explanations

14.7 Adverse Events recording

Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the investigator, whether believed by the investigator to be related or unrelated to the IMP, must be recorded on the AE information page of the CRF (for SAEs information must be recorded also on the "Serious Adverse Event Form").
The Investigator will also perform an evaluation with respect to seriousness and causality (relationship of any AE to IMP) of the AEs. and record it on the appropriate section of the CRF and on the "Serious Adverse Event Form" (if appropriate).

14.8 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: up to final study visit/ETV (observation window)

An AE occurring after the final visit/ETV and coming to knowledge of the investigator (e.g. during a follow-up assessment or by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator's judgment.

14.9 Adverse Events reporting

The official language for reporting is English. The investigator and clinical staff of the present study are familiar with English language.

The investigator must report to the CRO all AEs which occur during the study, regardless of their relationship to the IMP. Protocol specific AEs or laboratory abnormalities critical to safety

evaluations are to be identified in the protocol and reported to the sponsor according to reporting requirements and within the time periods specified.

All AEs are recorded by the investigator on the AE information page of the CRF.

In addition, SAE will have to be reported according to the following detailed procedure.

14.9.1 SAEs reporting

The investigator must report the SAEs to the CRO no later than 24 hours from when he/she becomes aware of the SAE, by Electronic Data Capture (preferred method), or e-mailing as scanned attachment (back up plan) or by faxing the "Serious Adverse Event Form" (back up plan) to the CRO, as stated in the "List of CRO/ personnel" in § 14.13 of this protocol.

The standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

Another copy of the "Serious Adverse Event Form" will be sent to the Medical Affairs/Clinical Operations for the Sponsor's file and another copy will be retained by the Investigator for the Investigator's file.

If the investigator becomes aware of any SAE occurred to a subject within the follow-up window established in the protocol, he/she will report the SAE as above. The SAE will be also reported in the CRF.

If outside the follow-up window established in the protocol the investigator becomes aware of a SAE, if the investigator judges that the SAE is related to the study drug, it should be reported to the Sponsor. The Investigator might use the "Serious Adverse Event Form" via email or fax, but the SAE must not to be reported in the CRF, as it is not an event occurred within the study period.

The investigator must report all SAEs that occur to the subjects to National Medical Products Administration/Local Ethics Committee/Provincial Food and Drug Administration/National Health and Family Planning Commission immediately no later than 24hours from when he/she becomes aware of SAE. Any SAEs that happen to the subjects outside the follow-up window should be reported by investigator to National Medical Products Administration/Local Ethics Committee/Provincial Food and Drug Administration/National Health and Family Planning Commission immediately.

14.10 Follow-up for Adverse Events

A follow-up "Serious Adverse Event Form" will be filled in if important follow-up information (i.e. diagnosis, outcome, causality assessment, results of specific investigations) is made available after submission of the initial AE Form for immediate reporting. Follow-up "Serious Adverse Event Form" will be reported to the Sponsor as above-described, under Section 14.9.1.

In any case of an AE that, in the opinion of the investigator, requires the subject's discontinuation, follow-up information relating to the subject's subsequent course must be collected until the event has subsided or the condition stabilised or when the subject is lost to follow up or death.

When follow-up data on non-serious AE are collected, information should be reported under "Comments" in the Final report of the CRF.

14.11 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the CRO/sponsor (day 0).
Fatal and life-threatening SUSARs, should be reported to Competent Authority as soon as possible and in any case within 7 days and to Ethics Committee per the requirement.
If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days. Complete follow-up report should be sent within 15 calendar days.
SUSARs which are not fatal and not life-threatening are to be reported to Competent Authority within 15 days and to Ethics Committee per the requirement.
The minimum information to be reported includes:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP (including active substance name, code)
- A causality assessment.

14.12 Other events qualified for expedited reporting

Other safety issues also qualify for expedited reporting may be sent to Competent authority when they might materially alter the current benefit-risk assessment of a medicinal product or would be sufficient to consider changes in the medicinal product administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the subject has completed a clinical trial and are reported to the investigator by the subject.
- new events relating to the conduct of the trial or the development of the medicinal product likely to affect the safety of the subjects, such as :
  - a SAE which could be associated with the trial procedures and which could modify the conduct of the trial

– a significant hazard to the subject population such as lack of efficacy of a medicinal product used for the treatment of a life-threatening disease
– a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical trials.

14.13 SAEs: contacts

The investigator will report any SAE to the CRO. The CRO's details for SAEs are the following:
Email: PPD

The sponsor's details for SAEs are the following:
Phone: PPD
Fax: PPD
Email: PPD

14.14 Pregnancy

Subjects must be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator, who must then withdraw the subject from the study without delay. The Investigator should also be notified of pregnancy occurring during the study but confirmed after its completion. In the event that a subject is subsequently found to be pregnant after inclusion in the study, then any pregnancy will be followed up to the end of pregnancy or pregnancy termination and the status of mother and child will be reported to the Sponsor after delivery through the Pregnancy Report Form provided by the Sponsor. The Investigator will send pregnancy reports to DSU within the timeframes of SAEs, with follow-up information to be actively sought for the outcome of pregnancy.

- Part I of the Form is completed at the time of awareness of foetal exposure during pregnancy.
- Part II of the Form is filled in when information on pregnancy outcome becomes available.

If pregnancy results in abnormal outcome (spontaneous miscarriage, stillbirth and congenital anomalies) will be considered as SAE. If the investigator considers this to be due to the IMP, this will be treated as an expedited ADR report.

15 DATA MANAGEMENT PROCEDURES

15.1 Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRFs. He/she must also check that the data reported in the eCRFs correspond to those in the subject's source documents.
ECG and laboratory results must be printed and signed by the Investigator and kept as source data on site after entering outcome into the eCRF.
All other data has to be documented in the subject file as source data first and then entered into the eCRF.
Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a subject visit, and monitors will have access to data recorded. These data will be reviewed

versus source documents by trial monitors for completeness and acceptability during monitoring visits.
If data correction is required for an eCRF after initial entry, the site personnel can make necessary corrections on their own or as a response to an automated query by the eCRF system. Monitor and Clinical Data Manager review the eCRF for accuracy and can also generate queries to the investigational staff for resolution.
Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

15.2 Database management

The CRO will update and verify the database and create the final SAS data sets. The final data file will be transferred to the sponsor in the agreed format with all the other study documentation.

15.2.1 Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities, AEs and previous and concomitant medications will be coded.
Information on coding dictionaries will be provided in a Data Management Plan.

16 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Monitoring

The monitoring visits will be conducted by personnel of the CRO, PAREXEL.

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements, CFDA-GCP and the monitoring plan.

Adequate time and availability for monitoring activities should be ensured by the investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the investigator will assure support to the monitor at all times.

The investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorised individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH-GCP and CFDA-GCP guidelines

16.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System that includes quality controls and audits at different study steps with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP and CFDA-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOAC principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete).

The clinical site(s) is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, CFDA GCP and any applicable regulatory requirement(s).

This protocol has been audited by the Sponsor QA.

The CROs and the sponsor will be responsible for their respective activities.

The sponsor may transfer any or all of the sponsor’s trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

16.3 Applicable SOPs

The sponsor, the clinical centre and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for Sponsor review, if required.

16.4 Data access

The investigator and the CRO(s) will ensure that all source data, medical records, CRFs and all other documentation that is relevant to this study will be made accessible for monitoring activities, audits, IEC review, and regulatory inspections.

16.5 Audits and inspections

The sponsors, independent bodies acting on behalf of the sponsor and the CRO have the right to perform audits according to ICH-GCP and CFDA responsibilities.

The study may also be inspected by regulatory authorities.

The investigator(s) and the CRO(s) agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorised individuals to have access to all the study documentation.

17 ETHICAL CONSIDERATIONS

17.1 Ethics and Good Clinical Practice (GCP)

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.

The approval of the study protocol by the relevant Ethics Committee will be obtained before the start of the study.
Study notification to the Competent Authorities will be performed according to the current local regulations.

The present clinical study will be carried out according to the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), CFDA Reg No. 25 "Good Clinical Practice (GCP) Mar 23, 2016 and the applicable local law requirements.

17.2 Informed consent

Before being enrolled into the clinical study, the subjects must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the EC and regulatory authorities. The document will include all the elements required by law according to the ICH-GCP recommendations.
In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organised
- the type of treatment (information on the IMP(s) and treatment procedures, as applicable)
- any potential negative effects attributable to the study product or treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of a subject insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded.

The investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the investigator and the subject.
A copy of the signed form will be given to the subject.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements. The investigator will allow inspection of the forms by authorised representatives of the sponsor, EC

members and regulatory authorities. He/she will confirm, by signing and dating the forms, that informed consent has been obtained.

17.3 Insurance policy

An insurance cover has been issued in favour of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

17.4 Withdrawal of subjects

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

17.4.1 Primary reason for discontinuation

- **Adverse event**: Any (significant) adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 14.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**: pregnancy is the state or condition of having a developing embryo or foetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

17.4.2 Discontinuation procedures

For any subject discontinuing the study, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory

assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening)

- arrange for alternative medical care of the withdrawn subject, if necessary
- record the subject decision about the use of collected biological samples
- report in the CRF date and time of the last dose administration, and date and primary reason of study discontinuation
- record in the CRF any follow-up, if the subject is withdrawn for an AE

Discontinued subjects will not be replaced.

17.5 Study termination

The study will be considered terminated at the date of the last visit of the last subject or upon completion of any follow-up procedure described in the protocol. The investigator and the sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately.

18 ADMINISTRATIVE PROCEDURES

18.1 Material supplied to the clinical centre

Beside the investigational products, the following study material will be supplied to the clinical centre:

- final version of the study protocol
- access to the eCRF
- copy of the SmPC relative to the investigational products
- informed consent forms
- investigator site file
- laboratory supplies

Moreover, before the start of the study, the investigator(s) will be provided with the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and study staff list form.

18.2 Protocol amendments

In order to obtain interpretable results, neither the investigator nor the sponsor will alter the study conditions agreed upon and set out in this protocol. Amendments should be made by mutual agreement between the investigator and the sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol.

All substantial amendments will be sent to the EC and concerned Competent Authorities, as appropriate. The amendment will be applicable only when it is approved, unless the changes consist of urgent safety measures to protect study subjects.

Non-substantial amendments will be notified according to the current local regulations.

18.3 Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

The investigator must keep source documents for each subject in the study. Information present on the CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including lab tests and ECG tracing, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP, CFDA GCP national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

18.4 Study subjects' recruitment

The CRO and its clinical site have detailed SOPs on the recruitment process.

18.5 Confidentiality and data protection

By signing this protocol, the investigator agrees to keep all the information provided by the sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the sponsor (protocols, CRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the sponsor to the investigator cannot be disclosed to others without direct written authorisation from the sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Subjects data collected in the eCRFs during the study will be documented in an anonymous way. If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the monitor, the sponsor and the investigator will be bound to keep this information confidential.

18.6 Publication policy

The Investigator agrees to inform Zambon in advance about his/her intention to divulge any data, results concerning the Confidential Information and/or the study patient to this Agreement. As a consequence hereof, the Investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon's rights to preserve and protect its

intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the study is conducted.

Furthermore, without any prejudice to the Investigator's right to divulge and save for what stated hereinabove, the Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the study hereto.

19 STUDY RESPONSIBLE PERSONS

19.1 Sponsor

Zambon S.p.A., via Lillo del Duca 10, 20091 Bresso (Milan), Italy
Phone: PPD
Fax: PPD

Protocol Review Committee Chairman
PPD , PPD

Medical Expert
PPD , PPD

19.2 Institutes performing the study

19.2.1 Clinical centre

"Denomination" Address XXXXXXX, "Zip" "City", China
Phone: +00.nnnnnnnnn
Fax: +00.nnnnnnnnn
Email: "Email"@"Specify".com

Principal investigator
"SpecifyName", MD

19.3 Drug assay

Analytical Facility for PK/drug assay:

United-Power Pharma Tech Co., Ltd. (UP-Pharma)
Building 30, Lane 908, Ziping Road, Pudong New Area, Shanghai, P.R.China
ZIP Code: 201318

Analytical facilities and procedures are in compliance with the general principles of GLP regulations.

19.4 Co-ordination, data analysis & reporting

PAREXEL International (IRL) Limited ("**PAREXEL**"), a corporation organized under the laws of Ireland with a registered address at 70 Sir John Rogerson's Quay, Dublin 2, Ireland.

19.5 Project Management and Monitoring

PAREXEL International (IRL) Limited ("**PAREXEL**"), a corporation organized under the laws of Ireland with a registered address at 70 Sir John Rogerson's Quay, Dublin 2, Ireland.

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21 APPENDIX 1

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
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]
Standardized 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
Alcohol breath test												
Urine pregnancy test (women)												x
ECG[6]												x
Inclusion/exclusion criteria												
Subject eligibility												
Enrolment and randomisation												
Confinement	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]	
Standardized meals[11]	x	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 after 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: standardized 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 Days 17: standardized breakfast
12. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*

CLINICAL TRIAL PROTOCOL

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

Phase I, single centre, single and multiple-dose, open-label, randomised, parallel-group, pharmacokinetics, safety and tolerability study

Protocol Code: Z7219J03

Date: 07 July 2020

Version: Final 3.0

Zambon SpA
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PROTOCOL AMENDMENT SUMMARY of CHANGES TABLE

DOCUMENT HISTORY		
Document	**Version**	**Date**
Amendment 2	Version 3.0	07 July 2020
Amendment 1	Version 2.0	18 April 2019
Original Protocol	Version 1.0	10 December 2018

PROTOCOL AMENDMENT n.2

The overall rationale for the changes implemented in the protocol amendment is to address study site considerations and local laboratory limitation, including drug dosage clarity, routine practice and windows for venous blood sampling, period for subject confinement in the clinical centre, and parameters for urinalysis. Part of these changes were earlier captured in clinical study protocol memorandums (dated 05 July 2019, 07 October 2019, and 15 January 2020). In addition, protocol amendment summary of changes table and protocol amendment history are added. Minor editorial changes were made throughout the text for abbreviations, punctuation, spacing, formatting, consistency, improvement of clarity, etc.

Substantial changes are detailed as follows:

Protocol section	**Description of Change**	**Rational for the change**
Section 1 STUDY SYNOPSIS Section 2 STUDY SCHEDULE Section 9.1 Study visits and procedures Section 9.2 Diet, lifestyle and study restrictions Section 21-Appendix 1	The descriptions for study procedures, study schedule, and diet, lifestyle, and study restrictions are revised as follows: (1) Wordings are added or revised to specify that subjects will be confined at the study centre throughout the study (Day 1 to Day 18). (2) The wordings indicating discharge on Day 3, Day 9, and Day 17 are removed. (3) The wording “returning of subjects” is removed for Visit 4 (Days 4 and 5), Visit 6 (Days 10 to 13), and Visit 8 (Day 18). (4) The wording “ambulatory visits” is removed for Visit 4 (Days 4 and 5). Visit 6 (Days 10 to 13), and Visit 8 (Day 18). (5) Standardized meal supplement is updated to cover the whole confinement period from Day -1 to Day 18 as follows: - Day -1: standardized dinner will be provided; - Days 1, 8, and 14: standardized lunch and dinner will be provided 5 h and 13 h after study drug administration;	To change the three subject confinement periods (Day -1 to Day 3, Day 8 to Day 9, and Day 14 to Day 17) to a total confinement (Day -1 to Day 18). This change is accompanied with standardized meal supplement throughout the confinement period.

	- Day 2 to Day 5: standardized breakfast (after PK sampling), lunch, and dinner will be provided; - Days 6 and 7: standardized breakfast, lunch, and dinner will be provided; - Day 9 to Day 13 and Day 15 to Day 17: standardized breakfast (after PK sampling), lunch, and dinner will be provided; - Day 18: standardized breakfast (after PK sampling) will be provided. (6) The tables for study schedule and the corresponding footnotes are updated to address points (1) to (5) listed above.	
Section 1 STUDY SYNOPSIS Section 2 STUDY SCHEDULE Section 9.1 Study visits and procedures Section 10.1.2 Vital signs Section 21-Appendix 1	Pre-dose and post-dose vital sign measurements are performed as follows: - Days 1, 8, and 14: pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min); - Days 5 and 18: at 96 h post-dose (± 15 min); - Day 10 to Day 13: pre-dose (before blood sampling and within 30 min of investigational product administration).	To specify the timing for pre-dose and post-dose vital sign measurements
Table 10.3.1.1, Section 10.3.1 Venous blood sampling	(1) The windows for venous blood sampling at 36- and 48-hours post-dose are changed from ± 10 min to ± 30 min. (2) The windows for venous blood sampling at 72- and 96-hours post-dose are changed from ± 10 min to ± 60 min.	To allow a wider tolerance range for venous blood sampling at 36-, 48-, 72-, and 96-hours post-dose.

Administrative changes are detailed as follows:

Protocol section	**Text of the protocol version 2.0**	**Amended text of the protocol version 3.0**	**Rational for the change**
Section 1 STUDY SYNOPSIS Section 6.1.2 Dosage regimen	**Cohort 1:** One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets	**Cohort 1:** One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets in	The descriptions for the study cohort 1 and cohort 2 are rephrased to avoid misunderstanding

	administered o.d. from day 8 to day 14. **Cohort 2:** One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 100 mg film-coated tablets administered o.d. from day 8 to day 14.	total from day 8 to day 14 and hence administered 1 tablet o.d. from day 8 to day 14. **Cohort 2:** One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 100 mg film-coated tablets in total from day 8 to day 14 and hence administered 1 tablet o.d. from day 8 to day 14.	for the study drug dosage.
Section 10.2 Clinical laboratory assays	**Urinalysis:** pH, specific gravity, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, leukocytes, erythrocytes, flat cells, crystals, cylinders.	**Urinalysis:** pH, specific gravity, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, leukocytes, erythrocytes, epithelial cells, crystals, cylinders.	To adjust the parameters for urinalysis by taking equipment limitation of the local laboratory into consideration.
Section 10.3.1 Venous blood sampling	Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20 I.U./mL Na-heparin. The first 2 mL of blood will be discarded at each collection time to avoid contamination of the sample with heparin. The remaining 8 mL will be collected from	Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution. The first 2 mL of blood will be discarded at each collection time. The remaining 6 mL will be collected from the catheter into blood collection tube (Li-heparin).	To revise the procedures for venous blood sampling to address that (1) sterile saline solution without Na-heparin is used as site routine practice to rinse cannula after each sampling and (2) blood will be directly collected into the evacuated blood collection tube containing anticoagulant

	the catheter and transferred with a syringe into heparinised tubes (Li-heparin).		(Li-heparin), as recommended by the World Health Organization (WHO) and used as site routine practice.

APPROVAL PAGE

Clinical Trial Title:	A phase I, pharmacokinetics, safety and tolerability study of single and multiple oral doses of safinamide in Chinese adult healthy volunteers.
Protocol Code	Z7219J03
Date:	07 July 2020
Author:	PPD
Sponsor Name and Address:	Zambon SpA Via Lillo del Duca 10 20091 Bresso, Milan, Italy

As agreed and approved:

_____/_____/_____	_____	_____
Date (dd/Mmm/yyyy)	**Principal Investigator**	**SIGNATURE**

Accepted for the Sponsor

PPD

1 STUDY SYNOPSIS

Title: A phase I, pharmacokinetics, safety and tolerability study of single and multiple oral doses of safinamide in healthy adult Chinese volunteers

Protocol number: Z7219J03

Clinical phase: Phase I

Study design: Phase I, single centre, single and multiple-dose, open-label, randomised, parallel-group, pharmacokinetics, safety and tolerability study

Planned nr. of centres / countries: 1/China

Investigator and centre: *Principal investigator*: TBD

Investigational products:
Test product 1: Xadago® 50 mg safinamide film-coated tablets, Zambon S.p.A., Italy
Test product 2: Xadago® 100 mg safinamide film-coated tablets, Zambon S.p.A., Italy

Dose regimen:
Subjects will be randomised 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) as follows:
Cohort 1: One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets in total from day 8 to day 14 and hence administered 1 tablet o.d. from day 8 to day 14.
Cohort 2: One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 100 mg film-coated tablets in total from day 8 to day 14 and hence administered 1 tablet o.d. from day 8 to day 14.

Study treatment is also summarised in the scheme below:

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

The investigational products will be orally administered in the morning, at 8:00±1h, under fasting conditions, with 240 mL (total volume) of still mineral water. A mouth-and-hand check will be performed immediately after dosing to ensure treatment compliance.

Objective: To evaluate safinamide pharmacokinetic profile, safety and tolerability after single and multiple dose administration to healthy adult Chinese volunteers.

End-points:
Primary end-point:
- To evaluate plasma safinamide pharmacokinetic parameters after single and multiple dose administration of the Test investigational products.

Secondary end-points:
- To collect safety and tolerability data after single and multiple dose administration of the Test investigational products.

Study variables:
Primary variables - Pharmacokinetics: The following safinamide PK parameters will be determined on day 1 (after the first dose), on day 8 (after the first multiple dose) and on day 14 (after the last dose):

After single dose and first multiple dose (day 1 and day 8):
- C_{max}: maximum safinamide plasma concentration
- t_{max}: time to achieve C_{max}
- AUC_{0-t}: area under the concentration-time curve from single dose administration to the last observed concentration time t, calculated with the linear up/log down trapezoidal method
- AUC_{0-24}: area under the concentration-time curve in the tau interval (from single dose administration to 24 h post-dose), calculated with the linear up/log down trapezoidal method

STUDY SYNOPSIS (cont.)

Study variables, continued: **Primary variables - Pharmacokinetics, continued:**

After single dose only (day 1):

- Kel: terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points
- $t_{1/2}$: apparent terminal elimination half-life, calculated, if feasible, as $\ln 2/K_{el}$
- $AUC_{0-\infty}$: area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration
- V_d/F: apparent volume of distribution associated with the terminal slope, calculated, if feasible, as $Dose/(AUC_{0-\infty}*K_{el})$
- Cl/F: apparent total body clearance, calculated, if feasible, as $Dose/AUC_{0-\infty}$
- MRT: Mean residence time calculated, if feasible, as $AUMC_{0-\infty}/AUC_{0-\infty}$, were $AUMC_{0-\infty}$ is area under the moment concentration-time curve extrapolated to infinity

After multiple dose (day 14):

- C_{max_ss}: maximum safinamide plasma concentration at steady-state
- t_{max_ss}: time to achieve $C_{max,ss}$
- C_{min_ss}: trough safinamide plasma concentration at steady-state, measured as concentration at 24h
- $AUCss_{0-t}$: area under the concentration-time curve at steady-state from the last dose administration to the last observed concentration time t, calculated with the linear up/log down trapezoidal method
- $AUCss_{0-24}$: area under the concentration-time curve at steady-state in the tau interval (from the last dose administration to 24 h post dose), calculated with the linear up/log down trapezoidal method
- C_{ave_ss}: average safinamide plasma concentration at steady-state, calculated as AUC_{ss0-24} /tau
- R: accumulation ratio, calculated as AUC_{ss0-24}/ Day 8 AUC_{0-24}
- DF%: peak-trough fluctuation over one dosing interval at steady-state, calculated as $(C_{max,ss} - C_{min,ss})/C_{ave,ss}*100$
- $V_{d,ss}/F$: apparent volume of distribution at steady-state associated with the terminal slope, calculated, if feasible, as $Dose/(AUCss_{0-24}*K_{el})$
- Cl_{ss}/F: apparent total body clearance at steady-state, calculated, if feasible, as $Dose/ AUCss_{0-24}$

Secondary variables - Safety and tolerability:

- Treatment emergent adverse events, vital signs (blood pressure, heart rate), body weight, physical examinations, clinical laboratory parameters, ECG.

Analytics: Plasma samples for safinamide determination will be collected 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**);
- pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (**day 8**)
- pre-dose on **days 10, 11, 12, 13**.

Analyses will be performed at a certified bioanalytical laboratory (to be designated). The analytical method will be detailed in the study analytical plan. Analytical facilities and procedures will be in compliance with the general principles of GLP regulations.

Safety evaluation: Safety of the study treatments will be evaluated on the basis of treatment-emergent adverse events, clinical safety laboratory tests, vital signs, ECGs, and physical examinations.
Adverse events will be collected throughout the study. Vital signs will be measured at screening, during the study and at final visit or early termination visit (ETV) in case of discontinuation. Physical examinations, ECGs and clinical laboratory tests will be performed at screening and final visit/ETV.

Sample size: Twelve (12) healthy male and female Chinese volunteers per 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 (1).

Main selection criteria:

Inclusion criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males and females, 18-45 year old inclusive
3. *Ethnicity:* Chinese

STUDY SYNOPSIS (cont.)

Main selection criteria, continued: Inclusion criteria, continued:

4. *Weight:* body weight ≥ 50 kg;
5. *Body Mass Index*: 19-26 kg/m^2 inclusive
6. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting/supine position
7. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. *No nicotine addiction (smoker subjects only)*: ability to abstain for smoking for the duration of the clinical study
9. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception during the study and two weeks post-dose:
   a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
   b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   c. A male sexual partner who agrees to use a male condom with spermicide
   d. A sterile sexual partner

   Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.
   For all women, pregnancy test result must be negative at screening and day -1.

Exclusion criteria:

1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; positive result on HIV, hepatitis B, (HBV) (except for vaccination), hepatitis C (HCV). Retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
6. *Medications*: medications, including over the counter medications, herbal remedies and traditional Chinese remedies for 2 weeks before the start of the study. In particular statins and HMG-CoA reductase inhibitors in the 2 weeks before the screening visit; medicinal products that are BCRP substrates; treatment with morphine or other similar opioids, whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives and antiepileptic drugs in the 4 weeks before the screening visit; treatment with any known enzyme inhibiting or inducing agent within 4 weeks preceding the screening visit. Hormonal contraceptives for women will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study
8. *Blood donation*: blood donations or blood components transfusion for 3 months before this study
9. *Abuse drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes or equivalent amount of tobacco per day within 3 months prior to day -1)
10. *Abuse drug test*: positive result at urine drug test at screening or day-1
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians; consumption of grapefruit or products containing grapefruit within 48 hours prior to the enrolment; consumption of beverages containing xanthines (e.g. coffee, tea, soda, coffee, milk, energy drinks) within 48 hours prior to the enrolment
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

STUDY SYNOPSIS (cont.)

Schedule:
Procedures and assessments during study visits are listed in the table below:

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Subjects' screening number assignment ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications check ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Clinical laboratory analyses: haematology, blood chemistry, urinalysis, serum virology and serum pregnancy test (women) ➢ Urine multi-drug kit test ➢ Adverse events check ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	
Period 1 Cohorts 1 and 2 - Visit 2	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Urine pregnancy test (women) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subjects' randomisation number assignment ➢ Adverse events and concomitant medications check	Day -1 Arrival at the clinical centre in the evening. Standardized dinner. Fasting for at least 10 h (overnight)
Period 1 Cohorts 1 and 2 - Visit 3	*Days 1 - 3*	Day 1 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min) Day 1 - Day 3 ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose ➢ AEs and concomitant medications check	Day 1 Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. Day 2 Standardized breakfast (after PK sampling), lunch and dinner Day 3 Standardized breakfast (after PK sampling), lunch, and dinner.

STUDY SYNOPSIS (cont.)

Study schedule, continued:			
Period 1 Cohorts 1 and 2 - Visit 4	*Days 4 - 5*	<u>Days 4 - 5</u> ➢ Blood sample collection for pharmacokinetic analysis at 72 h (day 4) and 96 h (day 5) post-dose ➢ AEs and concomitant medications check <u>Day 5</u> ➢ Vital signs measurement at 96 h post-dose (± 15 min) from Day 1	<u>Days 4 - 5</u> Subjects are to remain at the clinical centre throughout, with standardized breakfast (after PK sampling), lunch, and dinner.
A wash-out of 7 days will elapse between the single dose administered on Day 1 and the first multiple dose administered on day 8. All subjects will be confined in the clinical centre from Day -1 to the last visit on Day 18.			
Period 2 Cohorts 1 and 2 - Visit 5	*Days 8 -9*	<u>Day 8 - Day 9</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ AEs and concomitant medications check <u>Day 8 only</u> ➢ Vital signs measurement at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min)	<u>Day 8</u> Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. <u>Day 9</u> Standardized breakfast (after PK sampling), lunch, and dinner.
Period 2 Cohorts 1 and 2 - Visit 6	*Days 10 - 13*	<u>Days 10 - 13</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at pre-dose on each day ➢ Vital signs measurement pre-dose (before blood sampling and within 30 min of investigational product administration) ➢ AEs and concomitant medications check	<u>Days 10 - 13</u> Standardized breakfast (after PK sampling), lunch, and dinner.

STUDY SYNOPSIS (cont.)

Period 2 Cohorts 1 and 2 - Visit 7	*Days 14 - 17*	Day 14 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min) Day 14 - Day 17 ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose ➢ AEs and concomitant medications check	Day 14 Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. Days 15-16 Standardized breakfast (after PK sampling), lunch, and dinner. Day 17 Standardized breakfast (after PK sampling), lunch, and dinner.
Period 2 Cohorts 1 and 2 - Visit 8	*Day 18*	Day 18 ➢ Blood sample collection for pharmacokinetic analysis at 96 h post-dose ➢ Vital signs measurement at 96 h post-dose from Day 14 (± 15 min) ➢ AEs and concomitant medications check ➢ Final visit assessments (see below) and discharge	Day 18 Standardized breakfast (after PK sampling). Subjects will be discharged after final visit assessments (see Final visit/ETV below)
Final Visit/ETV	*Day 18. At ETV in case of early terminatio n*	The following final assessments will be performed after the 96-h time-point assessments (day 18) or at ETV in case of early discontinuation: ➢ Physical examination (body weight, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ Urine pregnancy test (women) Vital signs assessments performed at 96 h post-dose (± 15 min) on day 18 will be considered as the final assessment. Vital signs will also be measured at ETV, in case of early discontinuation. AEs and concomitant medications will also be checked at final visit/ETV. AEs will be captured up to the end of study visit. In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

STUDY SYNOPSIS (cont.)

Lifestyle and constraints:
During the study, the subjects will be confined from the evening preceding the first administration (study day -1) until the morning of day 18.

Subjects will be discharged from the study after final assessments, as specified above (Final visit/ETV).
The subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before investigational product administration. On days 1, 8 and 14, subjects will remain fasted up to 5 h post-dose. Standardized meals will be served at the clinical centre throughout the confinement period. Water will be allowed as desired, except for one hour before and one hour after investigational product administration. Coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement starting 48 h before the first administration until the end of the study. Smoking is not allowed for the whole study duration. Routine ambulant daily activities will be strongly recommended. Hazardous, strenuous or athletic activities will not be permitted.

Data analysis:
The data documented in this trial and the clinical parameters measured will be analysed using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.
Analysis set:
Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics
Safety set: all randomised subjects who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for the safety analyses.

PK set: all randomised subjects who fulfil the study protocol requirements in terms of investigational medicinal products intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the PK analysis.

Safety Assessments:
The statistical analysis of demographic and safety data will be performed using SAS®.
The safety and tolerability of the investigational products will be evaluated on the basis of treatment-emergent adverse events occurrence, laboratory tests and other safety assessments (see section above).
All adverse events, adverse drug reactions (ADR) and serious adverse events (SAEs), if applicable, will be coded using the Medical Dictionary for regulatory Activities and summarized by system organ class and preferred term, incidence, severity and relationship to study drug.
Pharmacokinetics:
The pharmacokinetic parameters will be calculated with a Non-Compartmental Analysis (NCA) using Phoenix WinNonlin v6.3 (or higher). Pharmacokinetic data will be listed and summarised by descriptive statistics.

Study duration:
Maximum study duration for both cohort 1 and 2 will be 32 days including screening period, study Period 1, washout and study Period 2.

2 STUDY SCHEDULE (A MORE DETAILED TABLE IS SHOWN IN APPENDIX 1)

ACTIVITIES		Period 1			Period 2				Final visit/ETV[1]
	Screening	Single Dose			Multiple Dose				
Visit	V1	V2	V3	V4	V5	V6	V7	V8	
Day	Day -14/-2	Day -1	Day 1/3	Day 4/5	Day 8/9	Day 10/13	Day 14/17	Day 18	Day 18[2]
Informed consent	x								
Demography	x								
Lifestyle	x								
Medical and surgical history	x								
Physical examination[3]	x								x
Prior and concomitant medications	x	x	x	x	x	x	x	x	x
Height	x								
Body Weight[3]	x								x
Laboratory analysis[4]	x								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)	x (Day 8: pre-dose, 2 hours post-dose)	x (daily from Day 10 to Day 13: pre-dose)	x (Day 14: pre-dose, 2 hours post-dose)	x (Day 18: 96 hours after Day 14)	x
Alcohol breath test		x							
Urine pregnancy test (women)		x							x
ECG[6]	x								x
Inclusion/exclusion criteria	x	x							
Subject eligibility	x	x							
Enrolment and randomisation		x							
Confinement		x	x	x	x	x	x		
Discharge								x	
Investigational product administration			x[7] (Day 1)		x[7]	x[7]	x[7] (Day 14)		
Blood sampling for PK analysis			x[8]	x[8]	x[9]	x[10]	x[8]	x[8]	
Standardized meals[11]		x	x	x	x	x	x	x	
Adverse event monitoring[12]	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 (before blood sampling and within 30 min of investigational product administration), at 2 h (± 15 min) and 96 h (± 15 min) after day 1 single dose and after day 14 last multiple dose. At pre-dose (before blood sampling and within 30 min of investigational product administration), and 2 h (± 15 min) after the day 8 first multiple dose. At pre-dose (before blood sampling and within 30 min of investigational product administration) on day 10 to day 13.*
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: standardized 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 to Day 5, Day 9 to Day 13, and Days 15 to 17: standardized breakfast (after PK sampling), lunch and dinner;
    Day 6 and Day 7: standardized breakfast, lunch, and dinner;
    Day 18: standardized breakfast (after PK sampling)
12. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*

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TABLES

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LIST OF ABBREVIATIONS

β-HCG	human chorionic gonadotropin β
γ-GT	γ-Glutamyl transpeptidase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOAC	Attributable-Legible-Contemporaneous-Original-Accurate-Complete
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from time zero to time t
$AUCss_{0-t}$ or $AUC_{0-t,ss}$	Area under the concentration-time curve at steady state
$AUC_{0-\infty}$	Area under the concentration vs. time curve up to infinity
AUC_{0-24h}	Area under the concentration-time curve in the tau interval
$AUCss_{0-24}$ or $AUC_{0-24h,ss}$	Area under the concentration-time curve at steady state in the tau interval
BUN	Blood Urea Nitrogen
BCRP	Breast Cancer Resistance Protein
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cl/F	Apparent total body clearance
C_{ave_ss}	Average drug concentration at steady state
C_{max}	Maximum drug concentration
C_{max_ss}	Maximum drug concentration at steady state
C_{mix_ss}	Trough drug concentration at steady state
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically Significant
CV	Coefficient of Variation
DF%	Peak-trough fluctuation over one dosing interval at steady-state
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IUD	Intra-Uterine Device
K_{el}	Terminal elimination rate constant
LLOQ	Lower Limit of Quantification
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit
MAO	Monoamino oxidase
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration

MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MW	Molecular Weight
N	Normal
NA	Not Applicable
NC	Not calculated
NCS	Not clinically significant
OTC	Over The Counter
PD	Parkinson's disease
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R_{acc}	Accumulation ratio
RBC	Red Blood Cells
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SNRI	Serotonin–norepinephrine reuptake inhibitors
SOC	System Organ Class
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test
T1	Xadago® 50 mg
T2	Xadago® 50 mg
TEAE	Treatment-Emergent Adverse Event
THC	Delta-9-tetrahydrocannabinol
$t_{1/2}$	Apparent terminal elimination half-life
t_{max}	Time to achieve C_{max}
V_d/F	Apparent volume of distribution associated with the terminal slope
WBC	White Blood Cells
WHO	World Health Organisation
WHODDE	World Health Organisation Drug Dictionary Enhanced

4 INTRODUCTION

4.1 Safinamide

4.1.1 Background

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 authorisation 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).

Safinamide uniquely combines potent, selective and reversible inhibition of monoamino oxidase B (MAO-B) with blockade of voltage-dependant Na^+ and Ca^{2+} channels and inhibition of glutamate release (4,8), thus showing a novel mode of action, targeting both dopaminergic and glutaminergic systems (9,10).
Data from Phase III clinical studies gave evidence that safinamide 50 or 100 mg/day improves the motor function in Parkinson's disease when prescribed as add-on therapy to dopamine agonists or L-dopa (3).

4.1.2 Clinical pharmacology and pharmacokinetics

Safinamide pharmacokinetics after single and multiple dose administrations have been described (11,12). At single ascending oral doses ranging from 2.5 to 10.0 mg/kg, safinamide was absorbed in a linear and dose-proportional fashion. Peak plasma levels were obtained on average at 1.8 to 2.8 h post-dose. Concentrations declined with a terminal half-life of 20 - 23h (11,12). Absolute bioavailability is high (95%), showing that safinamide is almost completely absorbed after oral administration and first pass metabolism is negligible (SmPC, 3). A complete long-lasting inhibition of platelet MAO-B activity was observed at all doses tested. Food intake prolonged the rate but did not affect the extent of safinamide absorption (11,12).
Studies in healthy volunteers (13,15) demonstrated that safinamide does not affect oral tyramine metabolism mostly mediated by the intestinal MAO-A, and confirm that it can be administered without tyramine-related dietary restrictions.

4.1.3 Safety

The overall safety profile of Xadago® is based on the clinical development program performed on over 3000 subjects, of which over 600 were treated for more than 2 years.

The most common side effects related to safinamide are dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension. Serious adverse reactions, such as hypertensive crisis (high blood pressure, collapse), neuroleptic malignant syndrome (confusion, sweating, muscle rigidity, hyperthermia, CPK increase), serotonin syndrome (confusion, hypertension, muscle stiffness, hallucinations), and hypotension, are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors.

With MAO-inhibitors there have been reports of drug interactions with concomitant use of sympathomimetic medicinal products. Impulse control disorders, pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments.

A complete list of adverse reactions observed with safinamide is presented in the SmPC (3).

4.2 Study rationale

The present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations (1).

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.

4.3 Risks and benefits

For AEs occurred with safinamide in previous clinical studies, please refer to § 4.1.3 and the SmPC (3). The most common side effects are dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension.

Based on the clinical experience, no particular risks are expected for the study subjects considering safinamide 50 mg and 100 mg multiple dose administrations.

5 STUDY OBJECTIVES

The objective of the study is to evaluate safinamide pharmacokinetic profile, safety and tolerability after single and multiple dose administration to healthy adult Chinese volunteers

5.1 Primary end-point

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

5.2 Secondary end-point

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

6 CLINICAL SUPPLIES

6.1 Treatment

6.1.1 Description of investigational products

TEST PRODUCT 1 (T1)	
Name	Xadago® 50 mg film-coated tablets
Active ingredient	Safinamide methanesulphonate (corresponding to 50 mg safinamide)
Marketing Authorization Holder	Zambon S.p.A., Italy
Pharmaceutical form	Film-coated tablets
Dose	Single 50 mg dose on day 1 Multiple 50 mg doses, once daily, for 7 days
Administration route	Oral

TEST PRODUCT 2 (T2)	
Name	Xadago® 100 mg film-coated tablets
Active ingredient	Safinamide methanesulphonate (corresponding to 100 mg safinamide)
Marketing Authorization Holder	Zambon S.p.A., Italy
Pharmaceutical form	Film-coated tablets
Dose	Single 100 mg dose on day 1 Multiple 100 mg doses, once daily, for 7 days
Administration route	Oral

6.1.2 Dose regimen

Subjects will be randomised 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 randomised, parallel-group design, as follows:

- Cohort 1: One (1) safinamide 50 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 50 mg film-coated tablets in total from day 8 to day 14 and hence administered 1 tablet o.d. from day 8 to day 14.

- Cohort 2: One (1) safinamide 100 mg film-coated tablet will be administered on day 1 followed by 7 safinamide 100 mg film-coated tablets in total from day 8 to day 14 and hence administered 1 tablet o.d. from day 8 to day 14.

Dose regimens are also summarised in the scheme below:

Table 6.1.2.1 Study dose regimen

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

6.1.3 Route and method of administration

The investigational products will be orally administered in the morning, at 8:00±1h, under fasting conditions, with 240 mL (total volume) of still mineral water.

A mouth-and-hand check will be performed immediately after dosing to ensure treatment compliance.

6.1.4 Investigational product distribution

All doses of the investigational products will be administered at the clinical centre by the investigator or by his/her deputy. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

6.2 Packaging and labelling

Packaging and labelling for the clinical study will be performed by a GMP compliant vendor, delegated by Zambon S.p.A., Italy.

Subjects' kit labelling will report all the information according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in The rules governing medicinal products in the European Community, Volume 4, 16), as follows:

a. Name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical study)

b. Pharmaceutical dosage form, route of administration, quantity of dosage units, and the name/identifier and strength/potency

c. The batch and/or code number to identify the contents and packaging operation

d. A study reference code allowing identification of the study, site, investigator and sponsor if not given elsewhere

e. A blank space for subject enrolment Nr. (to be reported by hand by the Investigator) and where relevant, the visit number

f. The name of the investigator (if not included in (a) or (d))

g. Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)

h. “For clinical study use only” or similar wording

i. The storage conditions

j. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity

k. "Keep out of reach of children"

The label will be in Chinese language.

6.3 Storage conditions

The investigational products will be stored at ≤ 25° C in a dry locked place, sheltered from light.

6.4 Drug accountability

The vendor delegated by Zambon S.p.A., Italy, will provide the clinical centre with a sufficient number of individual subject kits to conduct the study, plus sufficient reserve kits.

After receipt of the drug supply, the Pharmacist will confirm in writing by signing and dating standard drug accountability forms. At the end of the study, the drug product will be maintained in the original containers.

At the end of the study, used, unused and partially used supplies of the investigational products, provided by the vendor delegated by Zambon S.p.A., Italy, will be stored as detailed in § 6.3 above and then disposed of (upon sponsor written authorisation), after assessment of drug accountability.

7 INVESTIGATIONAL PLAN

7.1 Overall study design

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

7.2 Discussion of design

Following a specific request of CFDA, the present study will be part of safinamide registration package in China and was designed according to CFDA guideline recommendations (1).

Safinamide has recently been granted marketing authorization in EU, Norway and Switzerland on the basis of the results of clinical trials performed in European countries. 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.

Two single doses (i.e. 50 and 100 mg) of safinamide will be administered to two subject' cohorts. The study will continue with multiple administrations of safinamide 50 and 100 mg, orally taken once a day for 7 days.

The 50 and 100 mg oral doses have been selected according to the common clinical practice (see Xadago® SmPC). These doses were investigated in the previously performed Phase III clinical trials. The volunteers will be assigned to the two cohorts according to the study randomised, parallel-group design.

Safinamide pharmacokinetic profile will be investigated after single dose, according to CFDA guidance requirements, and at steady state since multiple doses are administered in the clinical practice. Safinamide steady state should be reached after 5 or 6 days of treatment (day 13-14 in this study). Safinamide pre-dose concentrations will be assessed before the last 5 doses (days 10-14).

An open design was chosen. However, no bias on study outcome is expected considering that the study PK endpoints are based on the objective measurement of safinamide in plasma.
Blood sampling time-points were selected on the basis of the known PK profile of safinamide. The sampling time lasts for about 4-7 elimination half-lives (mean PK half-life: 20-23 h) after both single dose and the last multiple dose administration.

8 STUDY POPULATION

8.1 Target population

Twenty-four (24) healthy male and female Chinese volunteers, aged 18-45 years inclusive, will be enrolled into the study.

8.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all these criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males and females, 18-45-year old inclusive
3. *Ethnicity:* Chinese
4. *Weight:* body weight ≥ 50 kg;
5. *Body Mass Index*: 19-26 kg/m^2 inclusive
6. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting/supine position
7. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
8. *No nicotine addiction (smoker subjects only)*: ability to abstain for smoking for the duration of the clinical study
9. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception during the study and two weeks post-dose:
    a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
    b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
    c. A male sexual partner who agrees to use a male condom with spermicide
    d. A sterile sexual partner

    Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.
    For all women, pregnancy test result must be negative at screening and day -1.

8.3 Exclusion criteria

Subjects meeting any of these criteria will not be enrolled in the study:

1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study

3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; positive result on HIV, hepatitis B (HBV) (except for vaccination), hepatitis C (HCV). Retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
6. *Medications*: medications, including over the counter medications, herbal remedies and traditional Chinese remedies for 2 weeks before the start of the study. In particular statins and HMG-CoA reductase inhibitors in the 2 weeks before the screening visit; medicinal products that are BCRP substrates; treatment with morphine or other similar opioids, whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives and antiepileptic drugs in the 4 weeks before the screening visit; treatment with any known enzyme inhibiting or inducing agent within 4 weeks preceding the screening visit. Hormonal contraceptives for women will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study
8. *Blood donation*: blood donations or blood components transfusion for 3 months before this study
9. *Abuse drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015-2020], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes or equivalent amount of tobacco per day within 3 months prior to day-1)
10. *Abuse drug test*: positive result at urine drug test at screening or day-1
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians; consumption of grapefruit or products containing grapefruit within 48 hours prior to the enrolment; consumption of beverages containing xanthines (e.g. coffee, tea, soda, coffee, milk, energy drinks) within 48 hours prior to the enrolment
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

8.3.1 Not allowed treatments

No medication, including OTC, herbal remedies and traditional Chinese remedies, will be allowed for 2 weeks before the start of the study and during the whole study duration.

Statins and HMG-CoA reductase inhibitors use will not be allowed for 2 weeks before and during the study. Wash-out interval for the treatment with morphine or other similar opioids,

whose concomitant use with MAO-B inhibitors is contraindicated, SSRIs, SNRIs, tri- or tetracyclic antidepressant, tramadol, pethidine, dextromethorphan, MAO inhibitors (e.g. selegiline), meperidine derivatives, antiepileptic drugs and the treatment with any known enzyme inhibiting or inducing agent or any investigational drugs intake will be at least 4 weeks before the screening visit. Hormonal contraceptives are allowed.

Paracetamol will be allowed as therapeutic counter-measure for adverse events (AEs) according to the investigator's opinion. The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the investigator, together with the sponsor, considers it could affect the study assessments or outcome.

9 STUDY SCHEDULE

The schedule of the study is summarised in Section 2.

9.1 Study visits and procedures

Each study subject completing the study will undergo 8 visits plus a final visit.

The study protocol foresees 2 periods: in the first one the investigational products are administered in single dose, in the second one in multiple doses. The single dose in the first period and the first dose in the second period are separated by a wash-out interval of 7 days. Maximum and minimum study duration will be 32 and 20 days, respectively, screening visit included.

The first subject first visit (FSFV) is defined as the 1st visit performed at the clinical centre by the 1st screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the clinical centre (or a telephonic follow-up, if applicable) by the last subject, i.e. the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – visit 1: between day -14 and day -2
  - Period 1 – visit 2: day -1

- **Interventional phase**
  - Period 1 – visit 3: days 1-3: single dose and blood sampling for PK analysis
  - Period 1 – visit 4: days 4-5: blood sampling for PK analysis
  - Wash-out interval of 7 days
  - Period 2 – visit 5: days 8-9: first multiple dose and blood sampling for PK analysis
  - Period 2 – visit 6: days 10-13: multiple doses and blood sampling for PK analysis
  - Period 2 - visit 7: days 14-17: last multiple dose and blood sampling for PK analysis
  - Period 2 - visit 8: day 18: blood sampling for PK analysis

- **Final phase**
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV)

Study schedule

	Day	Procedures/Assessments	Notes
Screening – Visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Subjects' screening number assignment ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications check ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Clinical laboratory analyses: haematology, blood chemistry, urinalysis, serum virology and serum pregnancy test (women) ➢ Urine multi-drug kit test ➢ Adverse events check ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	
Period 1 Cohorts 1 and 2 - Visit	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Urine pregnancy test (women) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subjects' randomisation number assignment ➢ Adverse events and concomitant medications check	<u>Day -1</u> Arrival at the clinical centre in the evening Standardized dinner. Fasting for at least 10 h (overnight)
Period 1 Cohorts 1 and 2 - Visit 3	*Days 1 - 3*	<u>Day 1</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min) <u>Day 1 - Day 3</u> ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose ➢ AEs and concomitant medications check	<u>Day 1</u> Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. <u>Day 2</u> Standardized breakfast (after PK sampling), lunch and dinner. <u>Day 3</u> Standardized breakfast (after PK sampling), lunch, and dinner.

Study schedule, continued

Period 1 Cohorts 1 and 2 - Visit 4	*Days 4 - 5*	<u>Days 4 - 5</u> ➢ Blood sample collection for pharmacokinetic analysis at 72 h (day 4) and 96 h (day 5) post-dose ➢ AEs and concomitant medications check <u>Day 5</u> ➢ Vital signs measurement at 96 h post-dose (± 15 min) from Day 1	<u>Days 4 - 5</u> Subjects are to remain at the clinical centre throughout, with standardized breakfast (after PK sampling), lunch, and dinner.
A wash-out of at least 7 days will elapse between the single dose administered on Day 1 and the first multiple dose administered on day 8. All subjects will be confined in the clinical centre from Day -1 to the last visit on Day 18.			
Period 2 Cohorts 1 and 2 - Visit 5	*Days 8 -9*	<u>Day 8 - Day 9</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ AEs and concomitant medications check <u>Day 8 only</u> ➢ Vital signs measurement at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min)	<u>Day 8</u> Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. <u>Day 9</u> Standardized breakfast (after PK sampling), lunch, and dinner.
Period 2 Cohorts 1 and 2 - Visit 6	*Days 10 - 13*	<u>Days 10 - 13</u> ➢ Investigational product administration at 08:00 ± 1 h; ➢ Blood sample collection for pharmacokinetic analysis at pre-dose on each day ➢ Vital signs measurement pre-dose (before blood sampling and within 30 min of investigational product administration) ➢ AEs and concomitant medications check	<u>Days 10 - 13</u> Standardized breakfast, (after PK sampling), lunch, and dinner.

Study schedule, continued

Period 2 Cohorts 1 and 2 - Visit 7	*Days 14 - 17*	Day 14 ➢ Investigational product administration at 08:00 ± 1 h; ➢ Vital signs measurement at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min) Day 14 - Day 17 ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose ➢ AEs and concomitant medications check	Day 14 Standardized lunch at approximately 5 h post-dose. Standardized dinner at approximately 13 h post-dose. Days 15-16 Standardized breakfast (after PK sampling), lunch and dinner. Day 17 Standardized breakfast (after PK sampling), lunch, and dinner.
Period 2 Cohorts 1 and 2 - Visit 8	*Day 18*	Day 18 ➢ Blood sample collection for pharmacokinetic analysis at 96 h post-dose ➢ Vital signs measurement at 96 h post-dose (± 15 min) from Day 14 ➢ AEs and concomitant medications check ➢ Final visit assessments (see below) and discharge	Day 18 Standardized breakfast (after PK sampling). Subjects will be discharged after final visit assessments (see Final visit/ETV below)
Final Visit/ETV	*Day 18. At ETV in case of early termination*	The following final assessments will be performed after the 96-h time-point assessments (day 18) or at ETV in case of early discontinuation: ➢ Physical examination (body weight, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ Urine pregnancy test (women) Vital signs assessments performed at 96 h post-dose (± 15 min) on day 18 will be considered as the final assessment. Vital signs will also be measured at ETV, in case of early discontinuation. AEs and concomitant medications will also be checked at final visit/ETV. AEs will be captured up to the end of study visit. In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

9.2 Diet, lifestyle and study restrictions

During the study, the subjects will be confined at the clinical centre from the evening preceding the first administration (study day -1) until the morning of day 18.

Subjects will be discharged from the study after final assessments (Final visit or ETV).

The subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before investigational product administration. On days 1, 8 and 14, subjects will remain under fasting conditions up to 5 h post-dose.
Standardized meals will be served at the clinical centre according to the schedule below:

- Day -1: standardized 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 to Day 5, Day 9 to Day 13, and Days 15 to 17: standardized breakfast (after PK sampling), lunch and dinner;
- Day 6 and Day 7: standardized breakfast, lunch and dinner;
- Day 18: standardized breakfast (after PK sampling).

Water will be allowed as desired, except for 1 h before and 1 h after investigational product administration. Coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement starting 48 h before the first administration until the end of the study. Smoking is not allowed for the whole study duration.

Routine ambulant daily activities will be strongly recommended. Hazardous, strenuous or athletic activities will not be permitted.

10 DESCRIPTION OF SPECIFIC PROCEDURES

10.1 Physical examination

Full physical examinations will be performed at screening and final visit/ETV. Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs.
All clinically significant abnormalities after the screening visit will be recorded as AEs.

10.1.1 Body weight

Body weight will be recorded at screening and final visit/ETV.
Subjects will be weighed (kg) lightly clothed without shoes. Height will be measured at screening only and Body Mass Index (BMI) will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

10.1.2 Vital signs

Subjects' blood pressure and heart rate will be measured by the investigator or his deputy after 5 min at rest (sitting/supine position) at the following times:

- at screening
- on day 1, day 8 and day 14: at pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h post-dose (± 15 min)
- on day 5 and day 18: at 96 h post-dose (± 15 min)
- on days 10-13: at pre-dose (before blood sampling and within 30 min of investigational product administration)
- at ETV (if applicable).

10.1.3 ECGs

12-Leads ECGs will be performed (supine position) at screening and final visit/ETV.

Date/time of the ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. Hard copies of the ECGs will be attached as source document at site.

10.2 Clinical laboratory assays

Samples of blood and urine will be collected. The following laboratory analyses will be performed at the screening visit:

HAEMATOLOGY

Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, haemoglobin (conv. units), haematocrit, MCV, MCH, MCHC, thrombocytes.

BLOOD CHEMISTRY
Electrolytes: sodium, potassium, calcium, chloride, inorganic phosphorus
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: total bilirubin, creatinine, glucose, urea or BUN, uric acid, total cholesterol, triglycerides
Proteins: total proteins

Serum pregnancy test (women).

URINE ANALYSIS
Urinalysis: pH, specific gravity, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, leukocytes, erythrocytes, epithelial cells, crystals, cylinders.

SERUM VIROLOGY
Hepatitis B (HBs antigen), **Hepatitis C** (HCV antibodies), **HIV 1/2** (HIV Ag/Ab combo).

A urine drug test will be performed at the clinical centre at screening, using a urine multi-drug kit. The following drugs will be assessed: cocaine, amphetamine, morphine, cannabis, benzodiazepines, barbital.

A serum pregnancy test will be performed by the laboratory at screening, as listed above. Urine pregnancy test will be performed on day -1 of each study period at the clinical centre and at the final visit/ETV.

The same analyses, with the exception of urine drug test and virology, will be performed at the final visit/ETV.

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be reported in the individual eCRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs.

10.3 Sampling for pharmacokinetic analysis

10.3.1 Venous blood sampling

Venous blood samples (up to 10 mL) will be collected from a forearm vein at the following times:

- At pre-dose (0 h), 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 (days 1-5) and the last multiple dose (days 14-18)
- At pre-dose on days 10-13
- At pre-dose (0 h) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose after the first multiple dose (days 8-9)

Actual sampling times for each subject will be recorded in the individual CRFs. The actual sampling times should not exceed the recommended tolerance ranges presented in the following table. Any deviation outside the recommended ranges will be verified through Data Clarification Forms and, if confirmed, will be reported as protocol deviation, although it will not automatically lead to the exclusion of the concerned subjects from the PK set.

Table 10.3.1.1 Tolerance ranges for the scheduled sampling times

Sampling time	Tolerance range
Pre-dose (0)	Within 30 minutes before investigational product administration
0.5 h (30 min)	± 1 min
1, 1.5 h	± 3 min
2, 3, 4 h	± 5 min
6, 8, 12, 16, 24 h	± 10 min
36, 48 h	± 30 min
72, 96 h	± 60 min

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution. The first 2 mL of blood will be discarded at each collection time.

The remaining 6 mL will be collected from the catheter into blood collection tube (Li-heparin). Samples handling and processing is described in study specific lab manual.

10.3.2 Analytics

The concentration of safinamide in plasma samples will be determined at a certified analytical laboratory (to be designated). Analyses will be performed according to the general Principles of "OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and GCP.

The method validation report and the analytical report will be attached to the final report.

10.3.3 Labelling, storage and transport of samples

10.3.3.1 Samples labelling

Labels and labelling process are described in the study specific lab manual.

10.3.3.2 Samples storage and transport

During the study the samples will be stored at ≤- 70° C. At the end of each collection day, aliquots 1 and 2 will be stored in separate freezers.

All aliquots 1, packed in sufficient dry ice, will be shipped by an authorised courier from the clinical centre (China) to the analytical laboratory.

11 ASSIGNMENT OF STUDY TREATMENT

11.1 Randomisation

Randomisation will be used to minimize bias in the assignment of subjects to treatment cohorts, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) will be evenly balanced across treatment cohorts.
The randomisation schedule will be computer-generated by the CRO biostatistician using SAS®.
The randomisation schedule will be attached to the final clinical study report.

11.2 Treatment allocation

Subjects will be randomised 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 randomised, parallel-group design.

On day -1, Period 1, subjects will be assigned a randomisation number, which will be used to assign the study treatment according to the randomisation schedule, as detailed above.
Subjects who prematurely discontinue participation after randomisation will not be replaced.

11.3 Blinding

This is an open study. No masking procedure will be applied.
The open label design is considered appropriate for the primary objective of pharmacokinetic characterization, because PK properties and assessments are not prone to bias of observation by the investigators or the subjects.

12 EVALUATION PARAMETERS

12.1 Study variables

12.1.1 Primary variables

The following safinamide PK parameters will be determined on day 1 (after the first dose), on day 8 (after the first multiple dose) and on day 14 (after the last dose):

After single dose and first multiple dose (day 1 and day 8)

- C_{max}, t_{max}, AUC_{0-t}, and AUC_{0-24h}

After single dose only (day 1):

- K_{el}, $t_{1/2}$, $AUC_{0-\infty}$, V_d/F, Cl/F and MRT

After multiple dose (day 14):

- C_{max_ss}, t_{max_ss}, C_{min_ss}, $AUC_{0-t,ss}$, $AUC_{0-24h,ss}$, C_{ave_ss}, R_{acc}, DF%, $Vd_{,ss}/F$ and $Cl_{,ss}/F$

12.1.2 Secondary variables

- Treatment emergent adverse events (TEAEs), vital signs (blood pressure, heart rate), body weight, physical examinations, clinical laboratory parameters, ECG.

12.2 Pharmacokinetic assessments

12.2.1 Pharmacokinetic parameters

The following safinamide PK parameters will be measured and/or calculated with a Non-Compartmental Analysis (NCA) using Phoenix WinNonlin v6.3 (or higher).

After single dose and first multiple dose (day 1 and day 8):

C_{max}:	Maximum safinamide plasma concentration
t_{max}:	Time to achieve C_{max}
AUC_{0-t}:	Area under the concentration-time curve from single dose administration to the last quantifiable concentration time t
AUC_{0-24h}:	Area under the concentration-time curve in the tau interval (from single dose administration to 24 h post dose)

After single dose (day 1):

K_{el}:	Apparent terminal elimination rate constant, calculated, if feasible, from the slope of a log-linear regression using at least 3 last concentration > LLOQ points
$t_{1/2}$:	Apparent terminal elimination half-life, calculated, if feasible, as $\ln 2/K_{el}$
$AUC_{0-\infty}$:	Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable drug concentration
V_d/F:	Apparent volume of distribution associated with the terminal slope, calculated, if feasible, as $Dose/(AUC_{0-\infty}*K_{el})$

Cl/F:	Apparent total body clearance, calculated, if feasible, as Dose/$AUC_{0-\infty}$
MRT:	Mean residence time, calculated, if feasible, as $AUMC_{0-\infty}/AUC_{0-\infty}$, were $AUMC_{0-\infty}$ is area under the moment concentration-time curve extrapolated to infinity

The sampling schedule is considered adequate if the ratio $AUC_{0-t}/AUC_{0-\infty}$ equals or exceeds a factor of 0.8 (i.e. if $\%AUC_{extra}$ is <20%) for more than 80% of the individual PK profiles. This assures that AUC_{0-t} covers a sufficient percentage of the theoretical total extent of exposure.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a determination coefficient $R^2 \geq 0.8$. Individual extrapolated parameters, when considered unreliable, will be reported as NC (not calculated).

After multiple dose (day 14):

C_{max_ss}:	Maximum safinamide plasma concentration at steady state
t_{max_ss}:	Time to achieve C_{max-ss}
AUC_{0-t},ss:	Area under the concentration-time curve at steady state from the last dose administration to the last quantifiable concentration time t
AUC_{0-24h},ss:	Area under the concentration-time curve at steady state in the tau interval (from the last dose administration to 24 h post dose)
C_{ave_ss}:	Average safinamide plasma concentration at steady state, calculated as AUC_{0-24h},ss /tau (24 h)
R_{acc}:	Accumulation ratio, calculated as $AUC_{0-24h,ss}$/ AUC_{0-24h}
DF%:	Peak-trough fluctuation over one dosing interval at steady-state, calculated as $(C_{max,ss} - C_{min,ss})/C_{ave,ss}*100$
$V_{d,}/F_{ss}$	apparent volume of distribution at steady-state associated with the terminal slope, calculated, if feasible, as Dose/(AUC_{0-24h},ss*K_{el})
$Cl_{,}/F_{ss}$	apparent total body clearance at steady-state, calculated, if feasible, as Dose/ AUC_{0-24h},ss

12.3 Safety assessments

Safety and general tolerability of the investigational products will be based on TEAEs, physical examinations, including body weight, vital signs, ECGs and routine haematology, blood chemistry and urinalysis laboratory tests.

13 STATISTICAL METHODS

The data documented in this study and the parameters measured will be evaluated using classic descriptive statistics, i.e. geometric mean, geometric CV (%) (PK data only), arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using Statistical Analysis Software (SAS®) Version 9.3 or higher.
The pharmacokinetic parameters will be calculated using the actual recoded sampling times and non-compartmental methods with Phoenix WinNonlin (Version 6.3 or higher).

13.1 Analysis Sets

13.1.1 Definitions

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 enrolment will be performed through randomised allocation to a treatment cohort. An eligible but not enrolled subject will be defined as a reserve.
A subject will be defined as randomised in the study when he/she is assigned to a randomised treatment cohort.

The following analysis sets will be considered:

- Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics.
- Safety set: all randomised subjects who receive at least one dose of the investigational medicinal product(s). This analysis set will be used for the safety analyses.
- PK set: all randomised subjects who fulfil the study protocol requirements in terms of investigational medicinal products intake and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the PK analysis.

Each subject will be coded as valid or not valid for the Randomised set, Safety set and PK set. Subjects will be evaluated according to the treatment they actually receive.

13.1.2 Reasons for exclusion from the PK set

Reasons for the exclusion of subjects from the PK set are the following:

Before bioanalysis

- vomiting and diarrhoea 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

If one of these events occurs, it will be noted in the CRF as the study is being conducted.

After bioanalysis

Exclusion of subjects on the basis of pharmacokinetic reasons is possible only for:

- subjects 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 $AUC_{0-\infty}$.
Any data excluded will be discussed in the CSR.

13.2 Sample size and power considerations

Twelve (12) healthy male and female Chinese volunteers / 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 (1).

13.3 Demographic, baseline and background characteristics

Demographic and background characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarised in contingency tables. Quantitative data will be summarised using classic descriptive statistics. The baseline will be the last pre-dose measurement.

13.4 Analysis of pharmacokinetic parameters

A descriptive PK will be presented. The results will be displayed and summarised in tables and figures. Individual and mean curves (+SD at nominal times), indicating inter-subject variability, will be plotted. Data below the lower limit of quantification (BLQ) will be

considered as 0 in the calculations and presented as BLQ in listings and tables. As a consequence of BLQ (i.e. 0) values, calculated geometric means (if requested) could be null. For this reason, in the presence of any null value, the geometric mean will be reported as not calculated (NC).

13.5 Safety and tolerability evaluation

13.5.1 Adverse events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).
AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of investigational product and not worsening after the first dose of investigational product.
- TEAEs: all AEs occurring or worsening after the first dose of investigational product

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship with investigational product and severity.

13.5.2 Physical examination

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed.

13.5.3 Laboratory data

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be listed. All laboratory results will be listed and a table of all the abnormal values will be presented.

13.5.4 Vital signs

Vital signs values will be listed and summarised by descriptive statistics.

13.5.5 Body weight

Body weight values will be listed and summarised by descriptive statistics.

13.5.6 ECG

Date/time of ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. Hard copies of the ECGs will be attached as source document at site.

14 DEFINITION AND HANDLING OF AEs AND SAEs

14.1 Applicable SOPs

AEs definition, classification and management will follow the CRO's SOPs, based upon applicable local and international regulations. The full SOPs or an operative summary will be made available in the CRO.

A brief summary of AE definition, classification and management is reported below.

14.2 Definition of Adverse Event (AE)

An Adverse Event is "*any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*".

AEs include:

- worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- patient/subject deterioration due to the primary illness
- intercurrent illnesses
- drug interactions
- events related or possibly related to concomitant medications
- abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

14.3 Definition of Adverse Drug Reaction (ADR)

An Adverse Reaction is "*any untoward and unintended response to an investigational medicinal product related to any dose administered*".
All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or matter to suggest a causal relationship.

- **Unexpected Adverse Drug Reaction**

An unexpected ADR is: "*An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (Reference Safety Information [RSI])*.

- **Reference Safety Information (RSI)**: in order to assess whether an adverse reaction is expected, the SmPC will be used.

14.4 Definition of Serious Adverse Events or Serious Adverse Drug Reaction

A Serious Adverse Event (SAE) is: "*any untoward medical occurrence or effect that at any dose*:

- results in death
- is life-threatening (i.e. the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but, according to appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

A **Serious Adverse Drug Reaction (SADR)** is an ADR that meets also the definition of SAE.

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is an ADR that is both unexpected (not consistent with the applicable product information, e.g. SmPC) and also meets the definition of a SAE.

A non-serious adverse event is any adverse event that does not meet the criteria listed above for a serious adverse event.

14.5 Definition of Severity of Adverse Events

The term "severe" is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the subject may experience slight discomfort.
- Moderate: causing some limitation of usual activities; the subject may experience annoying discomfort.
- Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

14.6 Definition of Adverse Event causality

Causality shall be determined according to the definition of ADR given in 14.3.

All AE judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor.

The following binary decision for causality will be used:

- Reasonable possibility that the IMP caused the event
- No reasonable possibility that the IMP caused the event

Features supportive of an association include:

- temporal plausibility
- pharmacological properties of the drug or of the substance class
- course of the adverse event after dechallenge and, if applicable, after rechallenge
- specific tests indicating involvement of the drug in the occurrence/worsening of the adverse event
- alternative explanations

14.7 Adverse Events recording

Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the investigator, whether believed by the investigator to be related or unrelated to the IMP, must be recorded on the AE information page of the CRF (for SAEs information must be recorded also on the "Serious Adverse Event Form").
The Investigator will also perform an evaluation with respect to seriousness and causality (relationship of any AE to IMP) of the AEs. and record it on the appropriate section of the CRF and on the "Serious Adverse Event Form" (if appropriate).

14.8 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: up to final study visit/ETV (observation window)

An AE occurring after the final visit/ETV and coming to knowledge of the investigator (e.g. during a follow-up assessment or by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator's judgment.

14.9 Adverse Events reporting

The official language for reporting is English. The investigator and clinical staff of the present study are familiar with English language.

The investigator must report to the CRO all AEs which occur during the study, regardless of their relationship to the IMP. Protocol specific AEs or laboratory abnormalities critical to safety

evaluations are to be identified in the protocol and reported to the sponsor according to reporting requirements and within the time periods specified.

All AEs are recorded by the investigator on the AE information page of the CRF.

In addition, SAE will have to be reported according to the following detailed procedure.

14.9.1 SAEs reporting

The investigator must report the SAEs to the CRO no later than 24 hours from when he/she becomes aware of the SAE, by Electronic Data Capture (preferred method), or e-mailing as scanned attachment (back up plan) or by faxing the "Serious Adverse Event Form" (back up plan) to the CRO, as stated in the "List of CRO/ personnel" in § 14.13 of this protocol.

The standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

Another copy of the "Serious Adverse Event Form" will be sent to the Medical Affairs/Clinical Operations for the Sponsor's file and another copy will be retained by the Investigator for the Investigator's file.

If the investigator becomes aware of any SAE occurred to a subject within the follow-up window established in the protocol, he/she will report the SAE as above. The SAE will be also reported in the CRF.

If outside the follow-up window established in the protocol the investigator becomes aware of a SAE, if the investigator judges that the SAE is related to the study drug, it should be reported to the Sponsor. The Investigator might use the "Serious Adverse Event Form" via email or fax, but the SAE must not to be reported in the CRF, as it is not an event occurred within the study period.

The investigator must report all SAEs that occur to the subjects to National Medical Products Administration/Local Ethics Committee/Provincial Food and Drug Administration/National Health and Family Planning Commission immediately no later than 24hours from when he/she becomes aware of SAE. Any SAEs that happen to the subjects outside the follow-up window should be reported by investigator to National Medical Products Administration/Local Ethics Committee/Provincial Food and Drug Administration/National Health and Family Planning Commission immediately.

14.10 Follow-up for Adverse Events

A follow-up "Serious Adverse Event Form" will be filled in if important follow-up information (i.e. diagnosis, outcome, causality assessment, results of specific investigations) is made available after submission of the initial AE Form for immediate reporting. Follow-up "Serious Adverse Event Form" will be reported to the Sponsor as above-described, under Section 14.9.1.

In any case of an AE that, in the opinion of the investigator, requires the subject's discontinuation, follow-up information relating to the subject's subsequent course must be collected until the event has subsided or the condition stabilised or when the subject is lost to follow up or death.

When follow-up data on non-serious AE are collected, information should be reported under "Comments" in the Final report of the CRF.

14.11 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the CRO/sponsor (day 0).
Fatal and life-threatening SUSARs, should be reported to Competent Authority as soon as possible and in any case within 7 days and to Ethics Committee per the requirement.
If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days. Complete follow-up report should be sent within 15 calendar days.
SUSARs which are not fatal and not life-threatening are to be reported to Competent Authority within 15 days and to Ethics Committee per the requirement.
The minimum information to be reported includes:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP (including active substance name, code)
- A causality assessment.

14.12 Other events qualified for expedited reporting

Other safety issues also qualify for expedited reporting may be sent to Competent authority when they might materially alter the current benefit-risk assessment of a medicinal product or would be sufficient to consider changes in the medicinal product administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the subject has completed a clinical trial and are reported to the investigator by the subject.
- new events relating to the conduct of the trial or the development of the medicinal product likely to affect the safety of the subjects, such as :
  - a SAE which could be associated with the trial procedures and which could modify the conduct of the trial

- a significant hazard to the subject population such as lack of efficacy of a medicinal product used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical trials.

14.13 SAEs: contacts

The investigator will report any SAE to the CRO. The CRO's details for SAEs are the following:
Email: PPD

The sponsor's details for SAEs are the following:
Phone: PPD
Fax: PPD
Email: PPD

14.14 Pregnancy

Subjects must be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator, who must then withdraw the subject from the study without delay. The Investigator should also be notified of pregnancy occurring during the study but confirmed after its completion. In the event that a subject is subsequently found to be pregnant after inclusion in the study, then any pregnancy will be followed up to the end of pregnancy or pregnancy termination and the status of mother and child will be reported to the Sponsor after delivery through the Pregnancy Report Form provided by the Sponsor. The Investigator will send pregnancy reports to DSU within the timeframes of SAEs, with follow-up information to be actively sought for the outcome of pregnancy.

- Part I of the Form is completed at the time of awareness of foetal exposure during pregnancy.
- Part II of the Form is filled in when information on pregnancy outcome becomes available.

If pregnancy results in abnormal outcome (spontaneous miscarriage, stillbirth and congenital anomalies) will be considered as SAE. If the investigator considers this to be due to the IMP, this will be treated as an expedited ADR report.

15 DATA MANAGEMENT PROCEDURES

15.1 Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRFs. He/she must also check that the data reported in the eCRFs correspond to those in the subject's source documents.
ECG and laboratory results must be printed and signed by the Investigator and kept as source data on site after entering outcome into the eCRF.
All other data has to be documented in the subject file as source data first and then entered into the eCRF.
Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a subject visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by trial monitors for completeness and acceptability during monitoring visits.
If data correction is required for an eCRF after initial entry, the site personnel can make necessary corrections on their own or as a response to an automated query by the eCRF system. Monitor and Clinical Data Manager review the eCRF for accuracy and can also generate queries to the investigational staff for resolution.
Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

15.2 Database management

The CRO will update and verify the database and create the final SAS data sets. The final data file will be transferred to the sponsor in the agreed format with all the other study documentation.

15.2.1 Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities, AEs and previous and concomitant medications will be coded.
Information on coding dictionaries will be provided in a Data Management Plan.

16 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Monitoring

The monitoring visits will be conducted by personnel of the CRO, PAREXEL.

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements, CFDA-GCP and the monitoring plan.

Adequate time and availability for monitoring activities should be ensured by the investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the investigator will assure support to the monitor at all times.

The investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorised individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH-GCP and CFDA-GCP guidelines

16.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System that includes quality controls and audits at different study steps with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP and CFDA-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOAC principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete).

The clinical site(s) is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, CFDA GCP and any applicable regulatory requirement(s).

This protocol has been audited by the Sponsor QA.

The CROs and the sponsor will be responsible for their respective activities.

The sponsor may transfer any or all of the sponsor’s trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

16.3 Applicable SOPs

The sponsor, the clinical centre and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for Sponsor review, if required.

16.4 Data access

The investigator and the CRO(s) will ensure that all source data, medical records, CRFs and all other documentation that is relevant to this study will be made accessible for monitoring activities, audits, IEC review, and regulatory inspections.

16.5 Audits and inspections

The sponsors, independent bodies acting on behalf of the sponsor and the CRO have the right to perform audits according to ICH-GCP and CFDA responsibilities.

The study may also be inspected by regulatory authorities.

The investigator(s) and the CRO(s) agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorised individuals to have access to all the study documentation.

17 ETHICAL CONSIDERATIONS

17.1 Ethics and Good Clinical Practice (GCP)

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.

The approval of the study protocol by the relevant Ethics Committee will be obtained before the start of the study.
Study notification to the Competent Authorities will be performed according to the current local regulations.

The present clinical study will be carried out according to the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), CFDA Reg No. 25 "Good Clinical Practice (GCP) Mar 23, 2016 and the applicable local law requirements.

17.2 Informed consent

Before being enrolled into the clinical study, the subjects must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the EC and regulatory authorities. The document will include all the elements required by law according to the ICH-GCP recommendations.
In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organised
- the type of treatment (information on the IMP(s) and treatment procedures, as applicable)
- any potential negative effects attributable to the study product or treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of a subject insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded.

The investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the investigator and the subject.
A copy of the signed form will be given to the subject.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements. The investigator will allow inspection of the forms by authorised representatives of the sponsor, EC

members and regulatory authorities. He/she will confirm, by signing and dating the forms, that informed consent has been obtained.

17.3 Insurance policy

An insurance cover has been issued in favour of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

17.4 Withdrawal of subjects

It will be documented whether or not each subject completed the clinical study. If, for a subject, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

17.4.1 Primary reason for discontinuation

- **Adverse event**: Any (significant) adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 14.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**: pregnancy is the state or condition of having a developing embryo or foetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

17.4.2 Discontinuation procedures

For any subject discontinuing the study, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory

assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening)

- arrange for alternative medical care of the withdrawn subject, if necessary
- record the subject decision about the use of collected biological samples
- report in the CRF date and time of the last dose administration, and date and primary reason of study discontinuation
- record in the CRF any follow-up, if the subject is withdrawn for an AE

Discontinued subjects will not be replaced.

17.5 Study termination

The study will be considered terminated at the date of the last visit of the last subject or upon completion of any follow-up procedure described in the protocol. The investigator and the sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately.

18 ADMINISTRATIVE PROCEDURES

18.1 Material supplied to the clinical centre

Beside the investigational products, the following study material will be supplied to the clinical centre:

- final version of the study protocol
- access to the eCRF
- copy of the SmPC relative to the investigational products
- informed consent forms
- investigator site file
- laboratory supplies

Moreover, before the start of the study, the investigator(s) will be provided with the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and study staff list form.

18.2 Protocol amendments

In order to obtain interpretable results, neither the investigator nor the sponsor will alter the study conditions agreed upon and set out in this protocol. Amendments should be made by mutual agreement between the investigator and the sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol.

All substantial amendments will be sent to the EC and concerned Competent Authorities, as appropriate. The amendment will be applicable only when it is approved, unless the changes consist of urgent safety measures to protect study subjects.

Non-substantial amendments will be notified according to the current local regulations.

18.3 Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

The investigator must keep source documents for each subject in the study. Information present on the CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including lab tests and ECG tracing, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP, CFDA GCP national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

18.4 Study subjects' recruitment

The CRO and its clinical site have detailed SOPs on the recruitment process.

18.5 Confidentiality and data protection

By signing this protocol, the investigator agrees to keep all the information provided by the sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the sponsor (protocols, CRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the sponsor to the investigator cannot be disclosed to others without direct written authorisation from the sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Subjects data collected in the eCRFs during the study will be documented in an anonymous way. If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the monitor, the sponsor and the investigator will be bound to keep this information confidential.

18.6 Publication policy

The Investigator agrees to inform Zambon in advance about his/her intention to divulge any data, results concerning the Confidential Information and/or the study patient to this Agreement. As a consequence hereof, the Investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon's rights to preserve and protect its

intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the study is conducted.

Furthermore, without any prejudice to the Investigator's right to divulge and save for what stated hereinabove, the Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the study hereto.

19 STUDY RESPONSIBLE PERSONS

19.1 Sponsor

Zambon S.p.A., via Lillo del Duca 10, 20091 Bresso (Milan), Italy
Phone: PPD
Fax: PPD

Protocol Review Committee Chairman
PPD

Medical Expert
PPD

19.2 Institutes performing the study

19.2.1 Clinical centre

"Denomination" Address XXXXXXX, "Zip" "City", China
Phone: +00.nnnnnnnnn
Fax: +00.nnnnnnnnn
Email: "Email"@"Specify".com

Principal investigator
"SpecifyName", MD

19.3 Drug assay

Analytical Facility for PK/drug assay:

United-Power Pharma Tech Co., Ltd. (UP-Pharma)
Building 30, Lane 908, Ziping Road, Pudong New Area, Shanghai, P.R.China
ZIP Code: 201318

Analytical facilities and procedures are in compliance with the general principles of GLP regulations.

19.4 Co-ordination, data analysis & reporting

PAREXEL International (IRL) Limited ("**PAREXEL**"), a corporation organized under the laws of Ireland with a registered address at 70 Sir John Rogerson's Quay, Dublin 2, Ireland.

19.5 Project Management and Monitoring

PAREXEL International (IRL) Limited ("**PAREXEL**"), a corporation organized under the laws of Ireland with a registered address at 70 Sir John Rogerson's Quay, Dublin 2, Ireland.

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21 APPENDIX 1

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
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	x	x	x
Investigational product administration			x[7]				
Blood sampling for PK analysis			x[8]	x[8]	x[8]	x[8]	x[8]
Standardized meals[11]		x	x	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
Alcohol breath test												
Urine pregnancy test (women)												x
ECG[6]												x
Inclusion/exclusion criteria												
Subject eligibility												
Enrolment and randomisation												
Confinement	x	x	x	x	x	x	x	x	x	x		
Discharge											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]	
Standardized meals[11]	x	x	x	x	x	x	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 (before blood sampling and within 30 min of investigational product administration), at 2 h (± 15 min) and 96 h (± 15 min) after day 1 single dose and after day 14 last multiple dose. At pre-dose (before blood sampling and within 30 min of investigational product administration) and 2 h (± 15 min) after the day 8 first multiple dose. At pre-dose (before blood sampling and within 30 min of investigational product administration) on day 10 to day 13.*
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 standardized 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 to Day 5, Day 9 to Day 13, and Days 15 to 17 standardized breakfast (after PK sampling), lunch and dinner;

    Day 6 and Day 7 standardized breakfast, lunch, and dinner;

    Day 18 standardized breakfast (after PK sampling)
12. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*