CLINICAL STUDY PROTOCOL

Study CRO-PK-22-359 - Sponsor code 22CH-Lrz05

Comparative bioavailability study of a new Lorazepam IBSA 2.5 mg orodispersible film vs. Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets in healthy volunteers under fasting conditions

Single centre, single dose, open-label, randomised, 3-way cross-over, pilot bioavailability study

Test product:	Lorazepam IBSA 2.5 mg orodispersible film, IBSA Institut Biochimique S.A., Switzerland
Reference product 1:	Tavor®, lorazepam 2.5 mg tablets, Pfizer Italia S.r.l.
Reference product 2:	Tavor®, lorazepam 2.5 mg orodispersible tablets, Pfizer Italia S.r.l.
Sponsor:	IBSA Institut Biochimique S.A., via del Piano 29, PO Box 266 CH-6915 Pambio-Noranco, Switzerland Phone: +41.58.360.10.00 Fax: +41.58.360.16.55 Email: sd@ibsa.ch
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Development phase:	Phase I
Version and date:	Final version 1.0, 16MAY2022

This study will be conducted in accordance with the current version of Good Clinical Practice (GCP), ICH topic E6 (R2)

This document comprises 60 pages

2 PROTOCOL APPROVAL

2.1 SPONSOR

IBSA Institut Biochimique S.A., Switzerland

Project Leader
Valeria Frangione, PhD, R&D Scientific Affairs Manager

16MAY2022 _____ Valeria Frangione
Date Signature

Drug Safety Manager and Medical Expert
Chiara Godina, EEA/UK QPPV

16 MAY 2022 _____ Chiara Godina
Date Signature

Gabriele Brunetti, MD, Medical Expert, EEA/UK Deputy QPPV

16.05.2022 _____ G Brunetti
Date Signature

Representative
Giuseppe Mautone, Head of R&D Scientific Affairs

16/05/2022 _____
Date Signature

2.2 INVESTIGATOR

Principal Investigator
I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki, the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable local law requirements, including supervising any individual or party to whom I will delegate trial-related duties and functions at the trial site.

Milko Radicioni, MD
CROSS Research S.A., Phase I Unit, Switzerland

16 MAY 2022
Date

Signature

2.3 CRO

CROSS Research S.A., Switzerland

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Quality Assurance Unit Representative
Mario Corrado, Quality Assurance Manager, Unit Head

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Date — Signature

3 STUDY SYNOPSIS

Title: Comparative bioavailability study of a new Lorazepam IBSA 2.5 mg orodispersible film vs. Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets in healthy volunteers under fasting conditions
Protocol number: CRO-PK-22-359 - Sponsor code 22CH-Lrz05
Clinical phase: Phase I
Study design: Single centre, single dose, open-label, randomised, 3-way cross-over, pilot bioavailability study
Planned nr. of centres / countries: 1/Switzerland
Investigator and centre: *Principal Investigator*: Milko Radicioni, MD; *Centre*: CROSS Research S.A., Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Investigational products: Test product (T): Lorazepam IBSA 2.5 mg orodispersible film, IBSA Institut Biochimique S.A., Switzerland Reference product 1 (R1): Tavor®, lorazepam 2.5 mg tablets, Pfizer Italia S.r.l. Reference product 2 (R2): Tavor®, lorazepam 2.5 mg orodispersible tablets, Pfizer Italia S.r.l.
Dose regimen: For each subject, a single dose of T, a single dose of R1 and a single dose of R2 will be administered under fasting conditions in three study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 7 days between the three consecutive administrations. The investigational products will be orally administered under fasting conditions on Day 1 of each study period at 08:00±1 h as follows: ➢ T: one orodispersible film of Lorazepam IBSA 2.5 mg without water ➢ R1: one tablet of Tavor® 2.5 mg with 150 mL of still mineral water ➢ R2: one orodispersible tablet of Tavor® 2.5 mg without water.
Objective: **Primary objective:** To compare the bioavailability of lorazepam in healthy men and women after single dose of T versus R1 and R2 products under fasting conditions. **Secondary objectives:** ➢ To describe the plasma pharmacokinetic parameters and profile of lorazepam after single dose of T, R1 and R2 products under fasting conditions ➢ To collect safety and tolerability data of the study treatments.
End-points: **Primary end-point:** ➢ To evaluate the rate (C_{max}) and extent (AUC_{0-t} and $AUC_{0-\infty}$, if feasible) of lorazepam absorption in plasma after single dose of T, R1 and R2 products under fasting conditions **Secondary end-points:** ➢ To describe the plasma pharmacokinetic parameters and profile of lorazepam after single dose of T, R1 and R2 products under fasting conditions ➢ To collect safety data after single dose of T, R1 and R2 products under fasting conditions.
Study variables: **Primary variables:** ➢ C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (if feasible) of plasma lorazepam after single dose of T, R1 and R2 products under fasting conditions **Secondary variables:** ➢ t_{max}, F_{rel} and, if feasible, $t_{1/2}$ and λ_Z of plasma lorazepam after T, R1 and R2 products under fasting conditions ➢ Treatment-emergent adverse events, vital signs (blood pressure, heart rate), physical examinations, body weight, clinical laboratory parameters, ECG.

STUDY SYNOPSIS (cont.)

Analytics: Lorazepam concentrations will be determined in plasma samples at Syneos Health Clinique Inc., Canada (or another laboratory if deemed necessary), using a fully validated LC-MS/MS method. Analyses will be performed in compliance with GCP regulations, following applicable GLP principles.

Sample size: Eighteen (18) healthy men and women will be enrolled in the study to have at least 12 completed subjects. Discontinued subjects will not be replaced up to a maximum of 6; if more than 6 subjects discontinue the study, possible replacement(s) will be discussed with the Sponsor on a case-by-case basis.
The sample size was not calculated by any formal statistical calculation. The planned sample size is estimated as sufficient for the exploratory purposes of this pilot study.

Safety assessments: Treatment-emergent adverse events; vital signs (blood pressure, heart rate); physical examinations including body weight; ECG; laboratory parameters.

Main selection criteria:
Inclusion criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: men and women, 18-55 years old inclusive
3. *Body Mass Index*: 18.5-30 kg/m^2 inclusive
4. *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 position
5. *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
6. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception:
    a. 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
    b. A male sexual partner who agrees to use a male condom with spermicide
    c. A sterile sexual partner

    Female participants 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; presence of mouth lesions or any other oral mucosa alteration; presence or history (within 28 days) of any tongue piercings; presence of any partials, braces or dentures
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle or formulations' ingredients or both; 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, immunological or neurological diseases that may interfere with the aim of the study
6. *Medications*: medications, including over the counter medications and herbal remedies for 2 weeks before the start of the study. Hormonal contraceptives for women will not be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
8. *Blood donation*: blood donations for 3 months before this study
9. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. *Drug test*: positive result at the drug test at screening

STUDY SYNOPSIS (cont.)

Main selection criteria (cont.):
Exclusion criteria (cont.)

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
13. *Pregnancy (women only)*: positive or missing pregnancy test at screening or Day -1, pregnant or lactating women.

Schedule:

		Day	Procedures/Assessments	Notes
Screening	**Visit 1**	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, physical abnormalities) ➢ Vital signs (blood pressure, heart rate) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis, virology ➢ Serum pregnancy test (women only) ➢ Drug screening test ➢ Adverse events monitoring ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source documents only and will not be transferred to the Sponsor
Period 1	**Visit 2**	*Day -1*	➢ Alcohol breath test ➢ Urine pregnancy test (women only) ➢ Vital signs (blood pressure, heart rate) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomisation (e.g., 001, 002, etc.) ➢ Adverse events and concomitant medications	Arrival at the Phase I Unit in the evening Confinement until the morning of Day 4 Standardised dinner Fasting overnight for at least 10 h
	Visit 3	*Day 1*	➢ Investigational product administration at 08:00±1h ➢ Vital signs (blood pressure, heart rate) measurement at pre-dose (0), 1.5 and 3 h post-dose ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0) and 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16 h post-dose ➢ Adverse events and concomitant medications	All subjects will be fasting for 5 h post-dose. Standardised lunch and dinner at approximately 5 and 12 h post-dose, respectively
	Visit 4	*Days 2-3*	➢ Vital signs (blood pressure, heart rate) measurement at 24 and 48 h post-dose ➢ Blood sample collection for pharmacokinetic analysis at: 24, 36 and 48 h post-dose ➢ Adverse events and concomitant medications	Standardised breakfast, lunch and dinner at approximately 08:00, 13:00 and 20:00 respectively

STUDY SYNOPSIS (cont.)

Schedule (cont.):				
		Day	**Procedures/Assessments**	**Notes**
Period 1	**Visit 5**	*Day 4*	➢ Vital signs (blood pressure, heart rate) measurement at 72 h post-dose ➢ Blood sample collection for pharmacokinetic analysis at 72 h post-dose ➢ Adverse events and concomitant medications	Discharge from the Phase I Unit in the morning, after the 72 h post-dose blood sample collection and vital signs check. Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions
Wash-out		*At least 7 days*	➢ A wash-out interval of at least 7 days will elapse between the two administrations of Periods 1 and 2	
Period 2	**Visit 6**	*Day -1*	➢ As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
	Visit 7	*Day 1*	➢ As Visit 3	As Visit 3
	Visit 8	*Days 2-3*	➢ As Visit 4	As Visit 4
	Visit 9	*Day 4*	➢ As Visit 5	As Visit 5
Wash-out		*At least 7 days*	➢ A wash-out interval of at least 7 days will elapse between the two administrations of Periods 2 and 3	
Period 3	**Visit 10**	*Day -1*	➢ As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
	Visit 11	*Day 1*	➢ As Visit 3	As Visit 3
	Visit 12	*Days 2-3*	➢ As Visit 4	As Visit 4
	Visit 13	*Day 4*	➢ As Visit 5	As Visit 5

STUDY SYNOPSIS (cont.)

Schedule (cont.):

	Day	Procedures/Assessments	Notes
Final Visit/ETV	*Day 4 of period 3 or ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ Vital signs (blood pressure, heart rate) (ETV only) ➢ ECG recording ➢ Laboratory analyses as at screening, with the exception of virology and pregnancy test ➢ Adverse events and concomitant medications In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization 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 reaction

Diet and lifestyle and study restrictions:
During each study period, the subjects will be confined at the Phase I Unit from the evening of Day -1 until the morning of Day 4. During confinement, the subjects will not take any food or drinks, except water, apart from the standardised meals. On Day -1 of each study period, a standardised low-fat dinner will be served, then all the subjects will remain fasted for at least 10 h (i.e., overnight). On Day 1 of each study period, the subjects will remain fasted until 5 h post-dose. Standardised lunch and dinner will be served at approximately 5 and 12 h post-dose. On days 2 and 3 of each study period, standardised breakfast, lunch and dinner will be served at about 08:00, 13:00 and 20:00, respectively.
Water will be allowed as desired, except for 1 h before and 1 h after investigational product administration (with the exception of water taken for treatments administration). To maintain an adequate hydration, the subjects will be encouraged to drink at least 150 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.
One cup of coffee or tea will be allowed after each meal only; any other coffee, tea or food containing xanthines (i.e., coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit will be forbidden from screening until the end of the study, while alcohol will be forbidden for 24 h before the first investigational product administration until the end of the study. One cigarette will be allowed after each meal.
During confinement, routine ambulant daily activities will be strongly recommended. For safety and pharmacokinetic reasons, subjects will be required to remain in a semi-supine position for the first 4 hours after drug administration. Hazardous, strenuous or athletic activities will not be permitted.

Data analysis:
The data documented in this study and the parameters measured will be presented using classic descriptive statistics, i.e., number of observations, geometric mean (pharmacokinetic data only), arithmetic mean, standard deviation, coefficient of variation, minimum, median and maximum values for quantitative variables, and frequencies (i.e., count and percentages) for qualitative variables. The statistical analysis will be performed using Phoenix WinNonlin® version 6.3 (or higher) and SAS® version 9.3 (TS1M1) or higher.
Analysis sets:
Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics.
Safety set: all subjects who receive at least one dose of the investigational medicinal product. This analysis set will be used for the safety analyses.
Pharmacokinetic set 1: all randomised subjects who fulfil the study protocol requirements in terms of T and R1 intake and have evaluable pharmacokinetic data readouts post-dose for the planned comparison of T vs. R1, with no major deviations that may affect the pharmacokinetic results. This analysis set will be used for the statistical comparison between T and R1 products administered under fasting conditions.
Pharmacokinetic set 2: all randomised subjects who fulfil the study protocol requirements in terms of T and R2 intake and have evaluable pharmacokinetic data readouts post-dose for the planned comparison of T vs. R2, with no major deviations that may affect the pharmacokinetic results. This analysis set will be used for the statistical comparison between T and R2 products administered under fasting conditions.

STUDY SYNOPSIS (cont.)

Pharmacokinetic analysis: A descriptive pharmacokinetic will be presented and the results will be displayed and summarised in tables and figures. PK parameters AUC_{0-t}, $AUC_{0-\infty}$ (if feasible) and C_{max} will be compared between T and R1 products and separately between T and R2 products, using analysis of variance. Before analysis, the data will be transformed using a neperian logarithmic transformation. The statistical analysis will take into account treatment, period, sequence and subject within sequence as fixed effects. T_{max} will be compared between treatments separately (T vs. R1 and T vs. R2) using the non-parametric Wilcoxon signed-rank test.
Demography and safety analysis: The analysis of demographic and safety data will be performed using SAS® version 9.3 TS1M1 (or higher).
Timing: EC meeting: JUN22; planned clinical phase: AUG-SEP22

4 STUDY SCHEDULE

ACTIVITIES	Screening	PERIOD 1, 2, 3 (wash-out≥7 days)				Final visit/ETV[15]
Visit	V1	V2, V6, V10	V3, V7, V11	V4, V8, V12	V5, V9, V13	
	Day -21/-2	Day -1	Day 1	Days 2-3	Day 4	Day 4[16]
Informed consent	x					
Demography	x					
Lifestyle	x					
Medical and surgical history	x					
Physical examination	x					x
Previous/concomitant medications	x	x	x	x	x	x
Height	x					
Laboratory analysis	x					x
Virology	x					
Pregnancy test	x[1]	x[2]				
Drug screening test	x					
Blood pressure and heart rate	x	x	x[7]	x[11]	x[13]	x[17]
ECG	x					x
Alcohol breath test		x				
Inclusion/exclusion criteria	x	x[3]				
Subject eligibility	x	x[3]				
Enrolment and randomisation		x[3]				
Confinement[4]		x	x	x		
Discharge					x[4]	
Investigational product administration			x[6]			
Blood sampling			x[8]	x[10]	x[13]	
Standardised meals		x[5]	x[9]	x[12]		
Adverse event monitoring[14]	x	x	x	x	x	x

1. *Women only - serum β-HCG test*
2. *Women only - urine test*
3. *Only at Visit 2*
4. *Confinement from Day -1 (evening) up to the morning of Day 4*
5. *Standardised low-fat dinner*
6. *On Day 1 at 8:00±1 h*
7. *At pre-dose (0), 1.5 and 3 h post-dose*
8. *At pre-dose (0) and 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16 h post-dose*
9. *Standardised lunch and dinner at approximately 5 and 12 h post-dose*
10. *At 24, 36 and 48 h post-dose*
11. *At 24 and 48 h post-dose*
12. *Standardised breakfast, lunch, and dinner approximately at 08:00, 13:00 and 20:00 respectively*
13. *At 72 h post-dose*
14. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/Early termination visit (ETV)*
15. *ETV in case of premature discontinuation*
16. *Final visit on Day 4 of Period 3 after the 72h post-dose blood sampling and vital signs check*
17. *At ETV only*

5 TABLE OF CONTENTS

5.1 TABLES

6 LIST OF ABBREVIATIONS

β-HCG	human chorionic gonadotropin β
γ-GT	γ-Glutamyl transpeptidase
λ_z	Terminal elimination rate constant
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from administration to the last observed concentration time t
$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity
$\%AUC_{extra}$	Percentage of the residual area (C_t/λ_z) extrapolated to infinity in relation to the total $AUC_{0-\infty}$
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CNS	Central Nervous System
CPL	Clinical Project Leader
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CS	Clinically Significant
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
DSU	Drug Safety Unit
EC	Ethics Committee
ECG	Electrocardiogram
eTMF	Electronic Trial Master File
ETV	Early Termination Visit
F_{rel}	Relative bioavailability
FSFV	First Subject First Visit
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISF	Investigator Study File
IUD	Intra-Uterine Device
LC-MS/MS	Liquid Chromatography Mass Spectrometry
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit

MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MD	Medical Director
MedDRA	Medical Dictionary for Regulatory Activities
N	Normal
NA	Not Applicable
NC	Not Calculated
NCS	Not Clinically Significant
ODF	Orodispersible film
OTC	Over The Counter
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R1	Reference product 1
R2	Reference product 2
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product
$t_{1/2}$	Half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to achieve C_{max}
USDA	United States Department of Agriculture
WHODDE	World Health Organisation Drug Dictionary Enhanced

7 INTRODUCTION

7.1 Background

Benzodiazepines are a class of drugs commonly prescribed for a wide range of anxiety-related conditions.

Lorazepam is a 1,4-benzodiazepine with antianxiety, sedative, and anticonvulsant effects. Like other benzodiazepine, lorazepam has high affinity to the gamma-aminobutyric acid (GABA) receptor complex, one of the most common neurotransmitters in the Central Nervous System (CNS). GABA has an inhibitory effect on the brain, reducing the excitability of neurons and producing a calming effect (1).

Consequentially to their mechanism of action, the benzodiazepines act as depressants of the CNS. The degree of CNS depression caused by a sedative should be the minimum consistent with therapeutic efficacy. The choice to use benzodiazepines should be studied carefully according to the origin of anxiety and the potential side-effects (2).

7.2 Pharmacokinetic (PK) of lorazepam

Following oral administration, lorazepam is almost completely absorbed from the gastrointestinal tract (95%). Plasma levels are dose-proportional. After a single dose of 1 mg of lorazepam, maximum plasma level ranges from 10 ng/mL to 15 ng/mL. Plasma peak concentrations are reached in 2-3 hours (3).

About 90% of the absorbed dose is bound to plasma proteins (3). The metabolization of lorazepam does not involve cytochrome P450 3A4 (CYP3A4) enzymes but consists in a simple one-step conjugation with glucuronic acid to form a pharmacologically inert glucuronide (3, 4).

Blood lorazepam levels decline thereafter, with an elimination half-life of about 12-16 hrs. About 85% of the administered dose is excreted as inactive glucuronide in the urine (3).

For further details, please refer to the study Investigator's Brochure (IB) (6).

7.3 Safety of Lorazepam IBSA formulation

Lorazepam is a well-known active substance with established efficacy and tolerability. Overall, lorazepam administered as a single oral dose to healthy subjects is safe and well tolerated.

The formulation under investigation, Lorazepam IBSA 2.5 mg orodispersible film (ODF), will be administered to men and women the first time in this clinical study. For further details, please refer to the study IB (6).

In any case, lorazepam 2.5 mg orodispersible formulations are already marketed and undesirable effects known. For more details, please refer to SmPC of reference products (5).

7.4 Rationale

The Sponsor, IBSA Institut Biochimique S.A., has developed a new ODF containing lorazepam, to provide an easy to take and rapidly dissolvable alternative to the marketed oral products for the short-term symptomatic treatment of anxiety and insomnia caused by anxiety, where the anxiety is severe, disabling or subjecting the individual to extreme distress.
Oral products containing lorazepam may also be used as premedication before diagnostic procedures, or before surgical interventions.

The Sponsor will investigate the bioavailability of the newly developed Lorazepam IBSA 2.5 mg ODF vs. Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets reference products, both marketed in Italy.

In details, the objective of the present single centre, single dose, open-label, randomised, 3-way cross-over, pilot study is to compare the bioavailability of lorazepam after a single dose of Lorazepam IBSA 2.5 mg ODF vs. each of two reference products, i.e., Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets, when administered to healthy men and women under fasting conditions.

7.5 Risks and benefits

On the basis of lorazepam safety profile (3, 4, 5), no potential risks are foreseen for the subjects enrolled in the present study.

Very common (i.e., ≥ 1/10) side-effects of lorazepam include daytime drowsiness, sedation and asthenia, while common (i.e., ≥ 1/100 and < 1/10) side-effects are depression, ataxia, confusion and muscle weakness. Furthermore, lorazepam should not be used during pregnancy since it may cause foetal damage. For other side-effects, refer to the IB (6).

The study involves blood samplings with cannula insertion, which may cause only minor discomfort. The risks associated with blood draws include pain, bleeding and bruising.

No potential benefits are foreseen for the subjects participating in this study.

8 STUDY OBJECTIVES

8.1 Primary objective

The primary objective of the study is to compare the bioavailability of lorazepam in healthy men and women after single dose of Lorazepam 2.5 mg ODF (T) vs. Tavor® 2.5 mg tablets (R1) and Tavor® 2.5 mg orodispersible tablets (R2) products under fasting conditions.

8.2 Secondary objectives

Secondary objectives of the study are the following:

- To describe the plasma PK parameters and profile of lorazepam after single dose of T, R1 and R2 products under fasting conditions
- To collect safety and tolerability data of the study treatments.

8.3 Primary end-point

- To evaluate the rate (C_{max}) and extent (AUC_{0-t} and $AUC_{0-\infty}$, if feasible) of lorazepam absorption in plasma after single dose of T, R1 and R2 products under fasting conditions

8.4 Secondary end-points

- To describe the plasma PK parameters and profile of lorazepam after single dose of T, R1 and R2 products under fasting conditions
- To collect safety data after single dose of T, R1 and R2 products under fasting conditions.

9 CLINICAL SUPPLIES

9.1 Treatment

Each subject will receive the three treatments (T, R1 and R2) in three consecutive study periods.

9.1.1 Description of products

The analytical certificates will be supplied with the Investigational Medicinal Products (IMPs).

9.1.1.1 Test product

IMP (T)	Lorazepam IBSA 2.5 mg ODF
Active substance	Lorazepam
Distributor	IBSA Institut Biochimique S.A., Switzerland
Manufacturer (active substance)	Cambrex Profarmaco Milano Srl, Italy
Manufacturer (finished product)	IBSA Farmaceutici Italia Srl, Italy
Pharmaceutical form	Orodispersible film
Dose	2.5 mg
Administration route	Oral

9.1.1.2 Reference products

IMP (R1)	Tavor® 2.5 mg tablets
Active substance	Lorazepam
Distributor	Pfizer Italia S.r.l.
Pharmaceutical form	Tablet
Dose	2.5 mg
Administration route	Oral

IMP (R2)	Tavor® 2.5 mg orodispersible tablets
Active substance	Lorazepam
Distributor	Pfizer Italia S.r.l.
Pharmaceutical form	Orodispersible tablet
Dose	2.5 mg
Administration route	Oral

The R1 and R2 products will be obtained from the Italian market.

9.1.2 Dose regimen

For each subject, a single dose of T, a single dose of R1 and a single dose of R2 will be administered under fasting conditions in three study periods, according to a 3-way cross-over

randomised design, with a wash-out interval of at least 7 days between consecutive administrations.

9.1.3 Route and method of administration

The IMPs will be orally administered under fasting conditions on Day 1 of each study period at 08:00±1h as follows:

- T: one orodispersible film of Lorazepam IBSA 2.5 mg without water
- R1: one tablet of Tavor® 2.5 mg with 150 mL of still mineral water
- R2: one orodispersible tablet of Tavor® 2.5 mg without water.

Just before the administration of T and R2 (orodispersible film and orodispersible tablet, respectively), the Investigator or deputy will take the orodispersible product out of packaging.

To avoid inadvertent breakages of T product, the Investigator or deputy shall:

1. take the envelope and hold it with the side not sealed facing up
2. gently peel both parts of the envelope and then hold each between his/her thumb and index fingers using one hand for each part
3. carefully tear both parts of the envelope in opposite directions until they will be separated.

The oral film will be visible and placed on one of the separated envelope parts.

To avoid inadvertent breakages of R2 product, the Investigator or deputy shall:

1. lift the lateral tab
2. remove the tab
3. take out the orodispersible tablet by pressing on the blister pouch.

The Investigator or deputy will place the orodispersible product directly on the subject's tongue. The Investigator will wear gloves during the administration procedure.

The orodispersible product will dissolve rapidly. Subjects will let the orodispersible product completely dissolve in their mouth. It must not be swallowed whole and must not be chewed or broken. The subject will be allowed to swallow saliva as the orodispersible product dissolves in the mouth.
In details, once the subject feels that the orodispersible product has completely dissolved, he/she will inform the Investigator who will inspect the subject’s mouth and verify the complete dissolution in the mouth. If the subject does not inform the Investigator within two minutes of the administration, his/her mouth will be checked by the Investigator at two and again at three minutes, if needed. If, upon inspection at two or three minutes, the orodispersible product is already dissolved, the time of mouth check will be recorded as dissolution end time. If the orodispersible product is not completely dissolved within 3 min, the subjects will be allowed to swallow without water. In this case, the dissolution end time will be considered as not applicable (NA).

For T and R2 treatments' administrations, the exact date and time of orodispersible product administration (defined as the time at which the orodispersible product is placed on the subject's tongue by the Investigator or deputy) and the time of complete dissolution of the orodispersible product (no residues present at inspection of the oral cavity by the Investigator or deputy) will be recorded. Dissolution times will be collected in specific source documents and subjects' Case Report Forms (CRFs).
For both treatments, the occurrence of inadvertent chewing and/or breaking and/or swallowing will be recorded.

For the administration of R1 product, the subject will swallow the tablet with 150 mL of still mineral water. The tablet must be swallowed whole and must not be chewed or broken. R1 product administration date and time will be recorded as well.

The Investigator or deputy will check that all subjects will take the IMPs appropriately.

9.1.4 Investigational product distribution

The IMPs will be administered by the Investigator or deputy. The IMPs will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

9.2 Packaging and labelling

The Sponsor will provide the Phase I Unit with 18 individual subject's kits and 6 reserve kits. Each kit will include a sachet of 1 Lorazepam IBSA 2.5 mg ODF, a blister of 20 Tavor® 2.5 mg tablets and a blister of 10 Tavor® 2.5 mg orodispersible tablets.
In case of issues with T, R1 or R2 products (i.e., IMP accidentally broken or fallen down), the Investigator can use the reserve product as follows:

- the second tablet of the same blister for the Tavor® 2.5 mg tablets product
- the second orodispersible tablet of the same blister for the Tavor® 2.5 mg orodispersible tablets product
- a new sachet containing 1 Lorazepam IBSA 2.5 mg ODF from one of the 6 reserve kits provided by the Sponsor.

The kit labelling will report all the information requested 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; 9) and according to the Annex VI of Clinical Trial Regulation (CTR), Labelling of Investigational Medicinal Products and Auxiliary Medicinal Products (8), as follows:

a. Name, address and telephone number of the Sponsor, contract research organization or Investigator (the main contact for information on the product and clinical study)

b. Pharmaceutical dosage form, route of administration, quantity of dosage units, 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. The study subject identification number

f. Only for reserve kits, an empty space, where the Investigator will handwrite the study subject identification number (screening number/randomisation number) in case of use

g. The name of the Investigator (if not included in (a) or (d))

h. Directions for use (refer to clinical study protocol)

i. "For clinical study use only" or similar wording

j. Storage conditions

k. 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.

Labels will be in English.

9.3 Storage conditions

All IMPs will be stored at room temperature (15-25°C) in a dry locked place, sheltered from light.

9.4 Drug accountability

The IMPs will be provided directly to the Investigator by the Sponsor, in excess of the amount necessary for the study (at least 25% excess).

After receipt of the IMP supply, the Investigator will confirm in writing by signing and dating standard drug accountability forms.

At the end of the study, used, unused and partially used supplies of IMPs provided by the Sponsor will either be destroyed on site (upon written authorization) or returned to the Sponsor, after assessment of drug accountability.

10 INVESTIGATIONAL PLAN

10.1 Overall study design

This is a single centre, single dose, open-label, randomised, 3-way cross-over, pilot bioavailability study.

10.2 Discussion of design

The present study has been designed taking into account the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1, 20 January 2010) (7).

The dose of 2.5 mg of lorazepam was chosen considering that it is the higher dosage available for oral lorazepam formulations in Europe (5).

The sample size was not calculated by any formal statistical calculation. The planned sample size is estimated as sufficient for the exploratory purposes of this pilot study.

Each randomised subject will be allocated to one sequence of treatments according to a computer-generated randomisation list (see § 14.2) and to the 3-way cross-over design.

An open-label design was chosen since the three formulations are different. However, no bias is introduced because the primary endpoint of the study is based on objective measurements of lorazepam in plasma. The outcome variables are not influenced by the subjects or Investigator being aware of the administered products.

Blood sampling time-points were selected on the basis of the known PK profile of lorazepam (3, 4).

Wash-out interval between subsequent administrations is based on lorazepam half-life (3).

Since lorazepam, like other benzodiazepines, can cause diminished cognitive functions and driving impairment, the subjects will be confined in the Phase I Unit until Day 4 (72 h post-dose).

11 STUDY POPULATION

11.1 Target population

The study population will include 18 healthy volunteers, men and women, aged 18-55 years inclusive.

11.2 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*: men and women, 18-55 years old inclusive
3. *Body Mass Index (BMI)*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure (SBP) 100-139 mmHg, diastolic blood pressure (DBP) 50-89 mmHg, heart rate (HR) 50-90 bpm, measured after 5 min at rest in the sitting position
5. *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
6. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception:
    a. A non-hormonal intrauterine device [IUD] 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
    b. A male sexual partner who agrees to use a male condom with spermicide
    c. A sterile sexual partner

    Female participants 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.

11.3 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; presence of mouth lesions or any other oral mucosa alteration; presence or history (within 28 days) of any tongue piercings; presence of any partials, braces or dentures
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness

4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle or formulations' ingredients or both; 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, immunological or neurological diseases that may interfere with the aim of the study
6. *Medications*: medications, including over the counter (OTC) medications and herbal remedies for 2 weeks before the start of the study. Hormonal contraceptives for women will not be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
8. *Blood donation*: blood donations for 3 months before this study
9. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025 (10)], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. *Drug test*: positive result at the drug test at screening
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
13. *Pregnancy (women only)*: positive or missing pregnancy test at screening or Day -1, pregnant or lactating women.

11.3.1 Not allowed treatments

No medication, including OTC and herbal remedies, will be allowed for 2 weeks before the start of the study and during the whole study duration. Hormonal contraceptives for women will not be allowed.

Paracetamol will be allowed as therapeutic countermeasure 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.

12 STUDY SCHEDULE

The schedule of the study is summarised at page 11.

12.1 Study visits and procedures

Each study subject will undergo 13 visits plus a final visit. The study protocol foresees 3 periods separated by wash-out intervals of at least 7 days. Minimum study duration will be 20 days, screening visit included. A written informed consent will be obtained before any study assessment or procedure.
The first subject first visit (FSFV) is defined as the 1st visit performed at the Phase I Unit by the 1st screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the Phase I Unit 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**
  - Visit 1: between Day -21 and Day -2
- **Interventional phase**
  - **Period 1**
  - Visit 2: Day -1
  - Visit 3: Day 1
  - Visit 4: Days 2-3
  - Visit 5: Day 4
  - Wash-out interval of at least 7 days
  - **Period 2**
  - Visit 6: Day -1
  - Visit 7: Day 1
  - Visit 8: Days 2-3
  - Visit 9: Day 4
  - Wash-out interval of at least 7 days
  - **Period 3**
  - Visit 10: Day -1
  - Visit 11: Day 1
  - Visit 12: Days 2-3
  - Visit 13: Day 4
- **Final phase**
  - Final visit/early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an ETV.

		Day	Procedures/Assessments	Notes
Screening	**Visit 1**	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, physical abnormalities) ➢ Vital signs (BP, HR) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis, virology ➢ Serum pregnancy test (women only) ➢ Drug screening test ➢ AEs monitoring ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source documents only and will not be transferred to the Sponsor
Period 1	**Visit 2**	*Day -1*	➢ Alcohol breath test ➢ Urine pregnancy test (women only) ➢ Vital signs (BP, HR) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomisation (e.g., 001, 002, etc.) ➢ AEs and concomitant medications	Arrival at the Phase I Unit in the evening Confinement until the morning of Day 4 Standardised dinner Fasting overnight for at least 10 h
	Visit 3	*Day 1*	➢ Investigational product administration at 08:00±1h ➢ Vital signs (BP, HR) measurement at pre-dose (0), 1.5 and 3 h post-dose ➢ Blood sample collection for PK analysis at: pre-dose (0) and 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16 h post-dose ➢ AEs and concomitant medications	All subjects will be fasting for 5 h post-dose. Standardised lunch and dinner at approximately 5 and 12 h post-dose, respectively
	Visit 4	*Days 2-3*	➢ Vital signs (BP, HR) measurement at 24 and 48 h post-dose ➢ Blood sample collection for PK analysis at: 24, 36 and 48 h post-dose ➢ AEs and concomitant medications	Standardised breakfast, lunch and dinner at approximately 08:00, 13:00 and 20:00 respectively
Period 1	**Visit 5**	*Day 4*	➢ Vital signs (BP, HR) measurement at 72 h post-dose ➢ Blood sample collection for PK analysis at 72 h post-dose ➢ AEs and concomitant medications	Discharge from the Phase I Unit in the morning, after the 72 h post-dose blood sample collection and vital signs check. Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions

		Day	Procedures/Assessments	Notes
Wash-out		*At least 7 days*	➢ A wash-out interval of at least 7 days will elapse between the two administrations of Periods 1 and 2	
Period 2	**Visit 6**	*Day -1*	➢ As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
	Visit 7	*Day 1*	➢ As Visit 3	As Visit 3
	Visit 8	*Days 2-3*	➢ As Visit 4	As Visit 4
	Visit 9	*Day 4*	➢ As Visit 5	As Visit 5
Wash-out		*At least 7 days*	➢ A wash-out interval of at least 7 days will elapse between the two administrations of Periods 2 and 3	
Period 3	**Visit 10**	*Day -1*	➢ As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
	Visit 11	*Day 1*	➢ As Visit 3	As Visit 3
	Visit 12	*Days 2-3*	➢ As Visit 4	As Visit 4
	Visit 13	*Day 4*	➢ As Visit 5	As Visit 5
Final Visit/ETV		*Day 4 of period 3 or ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ Vital signs (BP, HR) (ETV only) ➢ ECG recording ➢ Laboratory analyses as at screening, with the exception of virology and pregnancy test ➢ AEs and concomitant medications In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization 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 reaction

12.2 Diet and lifestyle

On Day -1 of each study period, a standardised low-fat dinner will be served, then all the subjects will remain fasted for at least 10 h (i.e., overnight).

On Day 1 of each study period, the subjects will remain fasted until 5 h post-dose. Standardised lunch and dinner will be served at approximately 5 and 12 h post-dose. On days 2 and 3 of each study period, standardised breakfast, lunch and dinner will be served at about 08:00, 13:00 and 20:00, respectively.

Water will be allowed as desired, except for 1 h before and 1 h after IMP administration (with the exception of water taken for treatments administration). To maintain an adequate hydration, the subjects will be encouraged to drink at least 150 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.

One cup of coffee or tea will be allowed after each meal only; any other coffee, tea or food containing xanthines (i.e., coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit will be forbidden from screening till the end of the study, while alcohol will be forbidden for 24 h before the first IMP administration until the end of the study. One cigarette will be allowed after each meal only.

During confinement, routine ambulant daily activities will be strongly recommended.

12.2.1 Restrictions

During each study period, the subjects will be confined at the Phase I Unit from the evening of Day -1 until the morning of Day 4.

During confinement, the subjects will not take any food or drinks, except water, apart from the standardised meals. For safety and PK reasons, subjects will be required to remain in a semi-supine position for the first 4 hours after drug administration.

Hazardous, strenuous, or athletic activities will not be permitted.

13 DESCRIPTION OF SPECIFIC PROCEDURES

13.1 Physical examination

Full physical examinations will be performed at the screening and final visit/ETV. Information about the physical examination will be recorded by the Investigator. Any abnormalities will be recorded.

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see § 17), will be recorded in the subject source documents.

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.

13.1.1 Body weight, height and BMI

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 BMI will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

13.1.2 Vital signs

Subjects BP and HR will be measured by the Investigator or deputy after 5 min at rest in sitting position at:

- Screening visit
- On Day -1 of each study period
- On Day 1 at pre-dose (0), 1.5 and 3 h post-dose of each study period
- On Day 2 at 24 h post-dose of each study period
- On Day 3 at 48 h post-dose of each study period
- On Day 4 at 72 h post-dose of each study period (the measurement on Day 4 of Period 3 will correspond to the final assessment)
- ETV

13.1.3 ECGs

12-Leads ECGs will be performed (in 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. Hard copies of the ECGs will be attached to the CRF.

13.2 Clinical laboratory assays

Samples of blood (12.5 mL) will be collected. The following laboratory analyses will be performed at the screening visit:

HAEMATOLOGY
Leukocytes and leukocyte differential count, erythrocytes, haemoglobin, 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, uric acid, total cholesterol, triglycerides
Proteins: total proteins

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

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 positive): leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria, glomerular erythrocytes.

The same analyses, with the exception of serum virology, will be performed at the final visit/ETV.

A urine drug screening test will be performed at the Phase I Unit at screening only.

A serum pregnancy test will be performed by the laboratory at screening. Urine pregnancy test will be performed on Day -1 of each study period at the Phase I Unit.

An alcohol test will be performed on Day -1 of each study period.

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 CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. Hard copies of the laboratory print-outs will be attached to the CRFs.

13.3 Sampling for PK analysis

13.3.1 Venous blood sampling

Venous blood samples (8 mL) will be collected from a forearm vein from Day 1 to Day 4 of each study period at the following times:

- pre-dose (0) and 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose

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 Table 13.3.1.1. Any deviation outside the recommended ranges will be verified through Data Clarification Forms (DCF) 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 Sets.

Table 13.3.1.1 Tolerance ranges for the scheduled sampling times

Sampling time	Tolerance range
Pre-dose (0)	Within 30 minutes before IMP administration
30 min (0.5 h)	± 1 min
1, 1.5	± 3 min
2, 2.5, 3, 3.5, 4, 5 h	± 5 min
6, 8, 12, 16, 24 h	± 10 min
36, 48 h, 72 h	± 30 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 6 mL will be collected from the catheter into 6 mL EDTA K_2 tubes by means a vacutainer blood transfer device.

After collection, blood samples will be stored on ice for a maximum of 60 min. Then the samples will be centrifuged at 4° C for 10 min at 2000±20 g to obtain plasma. Each plasma sample will be immediately divided into three aliquots, P1 (1 mL), P2 (1 mL), P3 (the remaining amount, if feasible), in pre-labelled polypropylene tubes, and stored frozen at ≤ - 20°C until analyses. The maximum time between the start of centrifugation and the storage of the aliquot will be 60 min.

If any clinical assessment, such as vital signs measurement or ECG recording, is foreseen at the same time-point as blood sampling for PK analysis, blood collection will be performed at the scheduled time. However, vital signs and ECG parameters can be influenced by the blood sampling. Therefore, these assessments can be performed within 30 min before the scheduled PK time-points. Any deviations outside the recommended time will be verified through DCFs. However, since vital signs measurements and ECG recordings will be performed for safety reasons only, deviations from the planned time schedule will be considered not relevant.

13.3.2 Analytics

The concentration of lorazepam in plasma samples will be determined at Syneos Health Clinique Inc., Canada (or another laboratory if deemed necessary), using a fully validated LC-MS/MS method.

Analyses will be performed according to the general Principles of "OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and applicable GCP regulations.

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

13.3.3 Labelling, storage and transport of samples

13.3.3.1 Samples labelling

Each sample tube will be clearly and unequivocally identified with a label resistant to the storage temperature and reporting:

Study code	Study CRO-PK-22-359 - Sponsor code 22CH-Lrz05
Subject number	001 to 018
Tube identification	P1/P2/P3
Study period	1/2/3
Scheduled sampling time	as h; see Table 13.3.1.1 at § 13.3.1

13.3.3.2 Samples storage and transport

At the Phase I Unit the samples will be stored at ≤ -20° C. At the end of each collection day, aliquots P1 and P3 and aliquots P2 will be stored in separate freezers.

All aliquots P1, packed in sufficient solid CO_2, will be shipped by an authorized courier from CROSS Research S.A. Phase I Unit, Switzerland, to the analytical laboratory, Syneos Health Clinique Inc., Canada (or another laboratory if deemed necessary). All aliquots will remain stored at the analytical laboratory for 3 months after the finalization of the bioanalytical report.
After that period, the Sponsor will decide to either destroy or return or store aliquots for an extended period under applicable fees as specified in the bioanalytical contract or service agreement.

The counter-samples (P2 and P3 aliquots) will remain stored at CROSS Research S.A., Switzerland. These samples could either be:

- sent to the laboratory for reanalysis should this become necessary for analytical reasons or if any problems occur during the delivery of P1 (or P2), or
- destroyed at an authorized site, or
- transferred to the Sponsor upon written request, or
- stored at CROSS Research S.A., for a maximum time of 5 years, or
- sent to a different laboratory for reanalysis should this become necessary for analytical reasons.

No analyses different from those stated in this protocol and agreed by the subjects when signing the informed consent form will be performed unless a new informed consent and a

new approval from the Ethical Committee (EC) is obtained. The subjects may ask to destroy their own samples at any time.

13.4 Total number of samples and blood withdrawn

During the study the following volume of blood will be collected:

For routine laboratories analysis:

Screening visit:	12.5 mL
Final visit/ETV:	12.5 mL

For PK analysis:

54 samples x 8 mL = 432 mL

In total 457 mL of blood (not exceeding a normal blood donation) will be withdrawn from each subject.

14 ASSIGNMENT OF STUDY TREATMENT

14.1 Randomisation

The randomisation list will be computer-generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of SAS® version 9.3 (TS1M1) (11) or higher (the actual version will be stated in the final report). The randomisation list will be supplied to Sponsor to prepare the Subject's kits. The randomisation list will be attached to the final clinical study report (CSR).

14.2 Treatment allocation

Subjects will be assigned to one of the possible sequences of the three treatments (T/R1/R2; R1/T/R2; R2/T/R1; R2/R1/T; T/R2/R1; R1/R2/T) according to the randomisation list and to the 3-way cross-over design.
Randomisation number will be given to the subjects on study Day -1, period 1, and will be used to assign the treatment sequence, as detailed above.

14.3 Blinding

This is an open study. The analytical laboratory will be in blind conditions.

15 EVALUATION PARAMETERS

15.1 Study variables

15.1.1 Primary variables

- C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (if feasible) of plasma lorazepam after single dose of T, R1 and R2 products under fasting conditions

15.1.2 Secondary variables

- t_{max}, F_{rel} and, if feasible, $t_{1/2}$ and λ_z of plasma lorazepam after T, R1 and R2 products under fasting conditions
- TEAEs, vital signs (BP, HR), physical examinations, body weight, clinical laboratory parameters, ECG.

15.2 PK assessments

15.2.1 PK parameters

The following PK parameters will be measured and/or calculated for plasma lorazepam, using the validated software Phoenix WinNonlin® version 6.3 (12) or higher (the actual version will be stated in the final report):

C_{max}:	Maximum plasma concentration
t_{max}:	Time to achieve C_{max}
λ_z:	Terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points
$t_{1/2}$:	Half-life, calculated, if feasible, as $\ln 2/\lambda_z$
AUC_{0-t}:	Area under the concentration-time curve from administration to the last observed concentration time t, calculated with the linear trapezoidal method
$AUC_{0-\infty}$:	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
$\%AUC_{extra}$:	Percentage of the residual area (C_t/λ_z) extrapolated to infinity in relation to the total $AUC_{0-\infty}$, calculated, if feasible as $100\times[(C_t/\lambda_z)/AUC_{0-\infty}]$
F_{rel}:	Relative bioavailability, calculated as ratio AUC_{0-t} (T)/AUC_{0-t} (R1) and ratio AUC_{0-t} (T)/AUC_{0-t} (R2)

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 $R^2 > 0.8$. Individual extrapolated parameters, when considered unreliable, will be reported as NC (not calculated).

15.3 Safety assessments

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

16 STATISTICAL METHODS

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

Not available data will be evaluated as "missing values". The analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (11) or higher (the actual versions will be stated in the CSR).
The statistical analysis of PK parameters will be performed using Phoenix WinNonlin® version 6.3 (12) or higher and SAS® version 9.3 (TS1M1) or higher (11).

16.1 Analysis Sets

16.1.1 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/exclusion criteria. Otherwise, he will be defined as a screen failure.

A subject will be defined as enrolled in the study if he/she is included in the interventional part of the study. The enrolment will be performed through randomised allocation to a treatment sequence.

An eligible but not enrolled subject will be defined as a reserve.

The following analysis sets will be defined:

- Randomised set: all randomised subjects. This analysis set will be used for demographic, baseline and background characteristics.
- Safety set: all subjects who receive at least one dose of IMP. This analysis set will be used for the safety analyses.
- PK set 1: all randomised subjects who fulfil the study protocol requirements in terms of T and R1 intake and have evaluable PK data readouts post-dose for the planned comparison of T vs. R1, with no major deviations that may affect the PK results. This analysis set will be used for the statistical comparison between T and R1 products administered under fasting conditions.
- PK set 2: all randomised subjects who fulfil the study protocol requirements in terms of T and R2 intake and have evaluable PK data readouts post-dose for the planned comparison of T vs. R2, with no major deviations that may affect the PK results. This analysis set will be used for the statistical comparison between T and R2 products administered under fasting conditions.

Each subject will be coded by the CRO Biometry Unit as valid or not valid for the Safety set and the PK sets. Subjects will be evaluated according to the treatment they actually receive.

16.1.2 Reasons for exclusion from the PK sets before bioanalysis

For each of the planned treatment comparisons, reasons for the exclusion of subjects from the PK sets are the following:

- 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.

16.1.3 Reasons for exclusion from the PK sets after bioanalysis

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

- subjects with lack of any measurable concentrations or only very low plasma concentrations for R1 (refer to PK set 1) or R2 (refer to PK set 2). A subject is considered to have very low plasma concentrations if his/her AUC is less than 5% of the R1 or R2 geometric mean AUC (which should be calculated without inclusion of data from the outlying subject)
- subjects with implausible concentrations (i.e., different from the known, expected concentration profiles) for the R1 or R2 medicinal product. The exclusion of these subjects must be justified on the basis of sound scientific reasons and mutually agreed between the CRO and the Sponsor
- subjects with non-zero baseline concentrations > 5% of C_{max}

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

16.2 Sample size and power considerations

Eighteen (18) healthy men and women will be enrolled in the study to have at least 12 completed subjects. Discontinued subjects will not be replaced up to a maximum of 6; if more than 6 subjects discontinue the study, possible replacement(s) will be discussed with the Sponsor on a case-by-case basis.
The sample size was not calculated by any formal statistical calculation. The planned sample size is estimated as sufficient for the exploratory purposes of this pilot study.

16.3 Demographic, baseline and background characteristics

Critical demographic 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.

16.4 Drug administration and analysis of dissolution time

For T and R2 treatments' administration, the date and time of orodispersible product placement and dissolution will be listed. R1 administration times will be listed as well. For all the three treatments, the occurrence of accidental chewing and/or breaking and/or swallowing (except for R1) will be listed. Administration time is defined as the time the orodispersible product is placed on the subject's tongue for T and R2 treatments.

16.5 Analysis of PK parameters

16.5.1 Descriptive PK

A descriptive PK will be presented. The results will be displayed and summarised in tables and figures. Individual and mean curves (+SD at sampling times), indicating inter-subject variability, will be plotted. Original data below the lower quantification limit (BLQL) will be considered as 0 in the calculations and presented as BLQL in listings and tables. As a consequence of BLQL (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).

16.5.2 Statistical comparison of PK parameters

PK parameters AUC_{0-t}, $AUC_{0-\infty}$ (if feasible) and C_{max} will be compared between T and R1 products and between T and R2 products, using analysis of variance (ANOVA). Before analysis, the data will be transformed using a neperian logarithmic transformation. The statistical analysis will take into account treatment, period, sequence and subject within sequence as fixed effects.

The 90% confidence intervals (CI) will be calculated for the point estimates (PE, i.e., the T/R1 and T/R2 ratio of least square geometric means) of the PK parameters.

T_{max} will be compared between treatments separately (T vs. R1 and T vs. R2) using the non-parametric Wilcoxon signed-rank test.

16.6 Safety evaluation

- **AEs**

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 AE (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring after informed consent signature by the enrolled subject but before the first dose of IMP and not worsening after the first dose of the IMP;
- TEAEs: all AEs occurring or worsening after the first dose of the IMP.

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 to treatment and severity.

- **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.

- **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. The overall Investigator's interpretation will be summarised using tables of frequency.

- **Vital signs**

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

- **Body weight**

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

- **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. The overall investigator's interpretation will be summarised using tables of frequency.

17 DEFINITION AND HANDLING OF AEs AND SAEs

17.1 Applicable SOPs

AEs definition, classification and management will follow the Sponsor SOP, based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the clinical centre.

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

17.2 Definitions

- **AEs and their classification**

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.

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

All AEs will be classified according to the categories **Serious/Non-Serious**, **Expected/Unexpected** and **Mild, Moderate** and **Severe**. In addition, the Investigator responsible for the subject will always be asked to indicate whether a causal relationship exists between the specified event and the study drug.

- **Adverse Drug Reaction (ADRs)**

All untoward and unintended responses to an IMP related to any dose administered.

All AEs assessed by either the reporting Investigator or 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 argument to suggest a causal relationship.

- **Serious AE/ADR**

A serious adverse event (SAE) or adverse reaction (SADR) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening (at the time of the event);
- requires patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is an important medical event: important medical occurrence that may not be immediately life-threatening or results in death or hospitalization but may jeopardize

the subject or may require intervention to prevent one of the other outcomes listed in the above definition must also usually be considered as serious.

The term "life-threatening" in the definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it would have been more severe.

Any AE/reaction which does not fall into the above categories is defined as not serious.

Surgical and other medical procedures themselves are not adverse events. They are therapeutic measures for conditions that required surgery/medical intervention. The condition for which the surgery/medical intervention is required is an adverse event, if it occurs or is detected during the study period. Planned treatments/surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

- **Unexpected AE/AR**

An unexpected adverse event/reaction is an adverse condition, the nature or severity of which is not consistent with the applicable and known product information as illustrated in the Reference Safety Information (RSI) section of the IB (6) for the T product and in the SmPC for the R1 and R2 products (5).

Adverse events/reactions that are adequately described in the RSI are to be considered expected.

- **PTAEs**

Any AE occurring after informed consent signature by the enrolled subject but before the first dose of IMP and not negatively affected by the first dose of IMP.

- **TEAEs**

Any AE occurring or worsening after the first dose of an investigational products

- **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A SAE for which there is evidence or argument to suggest a reasonable causal relationship according to the Investigator and/or to Sponsor: all SAEs for which the causal relationship with the study drug has been assessed as reasonable (which means by flagging the options "certain", "probable", or "possible").

17.3 Severity classification

Regardless of the classification of an AE as serious or non-serious, the severity of an AE will be rated according to the following definitions:

- **Mild**

Symptom barely noticeable to study subject and that does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom but may be given because of subject's personality.

- **Moderate**

Symptom of a sufficient severity to make study subject uncomfortable with influence on the performance of daily activities. The subject is able to continue the study, even if treatment for symptoms may be needed.

- **Severe**

Symptom causing severe discomfort. They may be of such severity that the study treatment has to be ended and the subject may be treated for symptoms and/or hospitalized.

It should be noted that the severity does not overlap the meaning of seriousness. Contrary to the other relevant definitions (seriousness, causality and expectedness), the classification of severity is not decisive for reporting purposes.

17.4 Causality assessment

The Investigator responsible for the subject must attempt to identify the cause of each adverse event and its relationship to study drug treatment. Jones' algorithm is used for the causality assessment. The relationship with the study drug will be classified as follows:

- **Certain**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
This means: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definite pharmacologically or phenomenologically* using a satisfactory re-challenge procedure if necessary.

* i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon (for instance, 'grey baby syndrome' and chloramphenicol, or anaphylaxis immediately after the administration of a drug that had been given previously). This means that, if this criterion is not met, the relationship between the drug administration and the event onset can never be classified as 'Certain', even in the case of a positive re-challenge.

- **Probable**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
This means: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent diseases or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge).

Re-challenge information is not required to fulfil this definition.

- **Possible**

There is some evidence to suggest a causal relationship; however, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant treatments).
This means: a clinical event, including laboratory test abnormality, with a reasonable time relationship to drug intake or application (topical forms), but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- **Unlikely**

There is another reasonable explanation for the event occurrence.
This means: a clinical event, including laboratory test abnormality, with a temporal relationship to drug intake that makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

- **Not related**

There is no evidence of any causal relationship.
This means: when sufficient information exists to indicate that the aetiology is unrelated to the study drug.

- **Pre-study treatment adverse event**

The causality assessment for PTAEs will not be expressed by the Investigator but with the option box "*pre-study treatment adverse event*", being obvious the relationship cannot stand, lacking the exposure to the IMP. IBSA Drug Safety Unit (DSU) will treat PTAEs as not reasonably related events.

After the causality assessment is performed the Investigator will evaluate expectedness, using the dedicated section (RSI) of IB for T and SmPC for R1 and R2.

17.5 Adverse events description and reporting

All the occurred AEs, independently of their classification, must be reported in the CRF, "adverse event" section.

All Serious Adverse Events (SAEs) which occur during the clinical trial, independently of their causal relationship, must be reported both in the CRF and also immediately (i.e., within 24 hours after first knowledge) by email or fax to:

IBSA – Drug Safety Unit (DSU)
Phone: +41.58.360.16.69
Fax: +41.58.360.16.95
Email: farmacovigilanza@ibsa.ch

using the dedicated form Serious Adverse Events Form (SAE form).

The collection period of AEs/SAEs for each subject starts from the subject's informed consent signature date until the end of the study.

When the Investigator has received knowledge of a SAE, he should fulfil a SAE form (Type of report: initial) with the support of the **Clinical Project Leader/Monitor**, if necessary, and send it to IBSA - DSU by fax or email as soon as possible but within 24 hours.

The preliminary notification should include, at least, this minimum information:

- Protocol number;
- Subject's identification (screening/randomisation number, age, gender);
- SAE/event description and its onset;
- Investigator's causality assessment on the relationship between event onset and the study medication used;
- IMP or batch N°, first administration and last administration before SAE;
- Outcome;
- Investigator: name, address, phone number.

Other important information to ensure a correct case evaluation:

- Detailed circumstances leading to SAE occurrence;
- Relevant medical history and concomitant medications taken during the study;
- Specific treatment of the SAE.

SAEs must be monitored until resolution or acceptable stabilization in the event of chronicity. In case of hospitalization is deemed necessary, a discharge card will be requested following SAE has been judged to be solved or anyway manageable in an outpatient fashion.
In case of death, the autopsy report will always be requested.

When the Investigator receives additional information regarding the initial SAE, he/she should fill in a new SAE form and tick the "Follow Up" box and fax or email it within 48 hours to the IBSA – DSU.

In case of **Suspected** (i.e., with a plausible causal relationship) **Unexpected Serious Adverse Reaction** (SUSAR) to the study drug, an **Expedited Reporting to Health Authorities and Ethic Committees by IBSA/CROSS Research is required,** so that the Investigator must collect to the fullest the information regarding the SUSAR, after evaluating the primary care to be delivered to the subject to preserve at first his health status. Should this happen, the Investigator must promptly inform IBSA-DSU within 24 h from its occurrence:

- **Fatal or life-threatening SUSARs** should be reported by IBSA to the Competent Authorities (concerned Health Authorities and Ethic Committees) as soon as possible but not later than **7 calendar days** from IBSA's first knowledge, followed by a follow-up report as complete as possible within **8 calendar days**.
- **All the other SUSARs** must be notified by IBSA to Competent Authorities (CAs) **within 15 calendar days**.

Relevant **follow-up information** for all SUSARs must subsequently be communicated **within an additional 15 days**.

The clock for expedited initial reporting (Day 0) starts as soon as the information containing the minimum reporting criteria (identifiable patient, identifiable reporter, adverse reaction and suspected IMP, causality, seriousness feature and expectedness) has been received by IBSA.

17.6 Follow-up

All AEs observed while subjects are on-protocol, regardless of classification, will be followed until resolution or acceptable stabilization in the event of chronicity.
All planned medical procedures, which are not completed as an action to counteract an adverse event occurred during the study procedures, will not be followed.

17.7 Pregnancy

In the event of pregnancy, when the Investigator receives knowledge of subject exposure to the drug, the Pregnancy Form, should be filled out by the Investigator and sent to DSU following the same timelines of SAE reporting. The pregnancy will be followed until delivery to ascertain both mother and baby are healthy.
In case, during pregnancy adverse events should arise, these AEs have to be specified within the Pregnancy Form itself. Furthermore, in case of SAE during pregnancy, a SAE form has to be completed and sent according to the modalities and timelines defined in section 17.5.

17.8 SAEs: contacts

The clinical site can be contacted using the phone and fax numbers stated in this protocol or calling the mobile phone number +41.79.822.35.07 (operative 24-h/day, 365 days/year). This mobile phone can be called by the study participants to communicate to the clinical staff any SAE occurring outside the clinical facility.

The contacts for SAEs are the following:
Dr. Milko Radicioni
Phone: +41.91.64.04.450
Fax: +41.91.64.04.451
Email: milko.radicioni@croalliance.com

18 DATA MANAGEMENT PROCEDURES

18.1 Data collection – CRFs

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the CRFs. He must also check that the data reported in the CRFs correspond to those in the subject's source documents.
To ensure eligibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the Investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections must be dated and initialled. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. The Investigator must provide a reasonable explanation for all missing data.
The CRFs will be completed, signed by the Investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the Sponsor.

18.2 Unique subject identifier

All the subjects who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the Sponsor study code (i.e., 22CH-Lrz05), the 3-digit site number (i.e., 001), the 4-digit screening number (e.g., S001, S002, etc.) and, if applicable, the 3-digit (or 4-digit in case of replacement) subject randomisation number (e.g., 001, 002, etc.). Study code, site number, screening number and subject randomisation number are separated by slashes ("/"). The last 8 digits (or 9-digit in case of replacement) of the unique subject identifier (enrolled subjects), corresponding to the subject screening and subject randomisation numbers separated by a slash, or the last 4 digits of the unique subject identifier (not enrolled subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the CSR.

18.3 Database management

The CRO will provide a double data entry with total re-entry of data by a second data entrist and discrepancy resolution by a third individual and 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.

18.3.1 Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™).
Previous and concomitant medications will be coded using the WHO Drug Dictionary Enhanced (WHODDE). The version of the coding dictionaries will be stated in the CSR.

19 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

19.1 Monitoring

The monitoring visits will be conducted by the appointed study CRA (§ 22.6) according to CROSS Research SOPs.

Monitoring activities, including monitoring purpose, selection and qualifications of monitor, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements and will be defined upon Risk Assessment and detailed in a Monitoring Plan.
As per IBSA SOPs, a remote bioanalytical monitoring session will be conducted by IBSA Bioanalytical Monitor.

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 authorized 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 guidelines.

19.2 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 the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOA+ principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete-Coherence-Enduring-Available).

The clinical site 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, and the applicable regulatory requirement(s).

The CRO and the Sponsor will be responsible for their respective activities.

The Sponsor may transfer any or all 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.

19.3 Applicable SOPs

The Sponsor, the Phase I Unit 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 review, if required. AEs, SAEs, SAE reconciliation and eTMF management will follow IBSA SOPs. ISF management will follow CRO SOP.

19.4 Data access

The Investigator and the CRO will ensure that all raw data records, 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.

19.5 Audits and inspections

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

The study may also be inspected by regulatory authorities.

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

20 ETHICAL CONSIDERATIONS

20.1 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 local (Canton Ticino) IEC and by the Federal Health Authorities (Swissmedic) will be obtained before the start of the study.

The present clinical study will be carried out according to the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable local law requirements.

20.2 Informed consent

Before being enrolled in 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. It 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 organized
- the type of treatment (information on the IMP 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 jeopardizing 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.

Subjects will be provided with an additional informed consent prepared in the local language by the CRO and already approved by the EC, regarding the information to the processing of personal data according to the Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates) and the European General Data Protection Regulation (GDPR, EU Regulation n 2016/679). Study subjects will sign this additional consent before study start. Furthermore, an additional informed consent regarding the information to the processing of personal data according to the Swiss Federal Law on Data Protection and the GDPR will be provided to the subjects by the Sponsor.

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 (see § 21.3). The Investigator will allow inspection of the forms by authorized representatives of the Sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.

20.3 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.

20.4 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.

20.4.1 Primary reason for discontinuation

- **adverse event**: any (significant) AE that in the opinion of the Investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 17.2.
- **death**
- **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**
- **protocol deviation**: an event or decision that stands in contrast to 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.

20.4.2 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, 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 up to a maximum of 6; if more than 6 subjects discontinue the study, possible replacement(s) will be discussed with the Sponsor on a case by case basis.

20.5 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 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 must be documented appropriately.

21 ADMINISTRATIVE PROCEDURES

21.1 Material supplied to the clinical centre

Beside the IMPs, the following study material will be supplied to the Phase I Unit:

- final version of the study protocol
- CRF for each subject plus some spare copies
- copy of the IB relative to the T product and SmPC for the R1 and R2 products
- informed consent forms

Moreover, before the start of the study, the Investigator 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.

21.2 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 Swissmedic, 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 regulations.

21.3 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. All information in 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 in 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) and in the agreed eTMF plan.

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 IMPs, 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 CSR.

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, national and international regulations. By signing the protocol, the Investigator and the Sponsor agree to adhere to these requirements.
Anyway once the storage period has elapsed, the Investigator must contact IBSA.
The Investigator is not allowed to destroy the study related documents without written authorization from IBSA. IBSA will inform the Investigator when such documents no longer need to be retained.

21.4 Study subjects' recruitment

Study participants will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enrol subjects in a new study. Before the start of the new study, the Principal Investigator and other relevant staff discuss with the volunteers' recruiter the study recruitment needs and specific requirements. On the basis of this information, the volunteers' recruiter queries the database, contacts potential participants to propose the study and evaluate their interest and availability. In addition to the volunteers' database, new subjects often call or email the CRO asking to become a research volunteer, after hearing of the clinical site activities from other volunteers or friends or after checking the company web site.

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

21.5 Confidentiality and data protection

By signing this protocol, the Investigator and the CRO agree to keep all the information provided by the Sponsor in strict confidentiality and to request the same confidentiality from their staff. Study documents provided by the Sponsor (protocols, IB, CRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the Sponsor to the Investigator and to the CRO cannot be disclosed to others without direct written authorization from the Sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Data on subjects collected in the CRFs during the study will be documented in a coded way (§ 18.2).
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.

21.6 Publication policy

The Sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the Investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases.
Study results will be communicated in full to the competent Health Authorities by the submission of a complete CSR.

As the Sponsor agrees that the study results can be published by the Investigator, the Investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the Sponsor before any public disclosure.
This will be done to ensure that clinical study results are reported in an objective, accurate and balanced manner. The Sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30-90 days in relation with the complexity of the work).

The Investigator will also be provided by the Sponsor with the CSR and the results of any additional analysis, tables, figures, etc. undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).
On an exceptional basis, the Sponsor may temporarily delay registration of certain data elements (e.g., compound, name, outcome, measures, etc.) to seek necessary intellectual property protection. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

According to The Federal Act on Research involving Human Beings and the Ordinance on Clinical Trials in Human Research, the study will be registered and published in a WHO primary register or clinicaltrials.gov as well as in the supplementary federal database.

22 STUDY RESPONSIBLE PERSONS

22.1 Sponsor

IBSA Institut Biochimique S.A., Via del Piano 29, PO Box 266, CH-6915 Pambio-Noranco, Switzerland
Phone: +41.58.360.10.00
Fax: +41.58.360.16.55
Email: sd@ibsa.ch

Sponsor Representatives
Valeria Frangione, PhD, R&D Scientific Affairs Manager
Giuseppe Mautone, Head of R&D Scientific Affairs

Drug Safety Manager and Medical Expert
Chiara Godina, EEA/UK QPPV
Gabriele Brunetti, MD, Medical Expert and EEA/UK Deputy QPPV

22.2 Institutes performing the study

22.2.1 Clinical centre

CROSS Research S.A. - Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
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Fax: +41.91.64.04.451
Email: clinic@croalliance.com

Principal Investigator
Milko Radicioni, MD

22.3 Drug assay

Syneos Health Clinique Inc.
2500, Einstein Street,
Québec (Québec), G1P 0A2, Canada
Phone: +1.418.5274000
Email: alexandre.tremblay@syneoshealth.com

Analytics representative
Alexandre Tremblay, Manager, Bioanalysis (Principal Investigator), Early Phases

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

22.4 Centralized clinical laboratory

Unilabs Ticino, via Rovere 8, CH-6932 Breganzona, Switzerland
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22.5 Coordination, data analysis & reporting

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Medical Writer
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Biometry Unit Representative
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Email: statistics@croalliance.com

Quality Assurance Unit Representative
Mario Corrado, Quality Assurance Manager, Unit Head
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22.6 Monitoring

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Bioanalytical monitor

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Elisa Bettazzi, Bioanalytical Monitoring Specialist
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23 REFERENCES

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4. SmPC (Summary of Product Characteristics) Lorazepam 2.5mg Tablets, Jan 2021, https://www.medicines.org.uk/emc/product/6138/smpc#gref
5. SmPC Tavor® 1 mg and 2.5 mg tablets, Tavor® 1 mg and 2.5 mg orodispersible tablets and Tavor® 2 mg/ml oral drop, Pfizer Italia S.r.l., 27 August 2019, https://farmaci.agenziafarmaco.gov.it
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9. Guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.
10. U.S. Department of Health and Human Services and U.S. Department of Agriculture, Nutrition and your health: 2020-2025 Dietary Guidelines.
11. SAS/STAT® User's Guide.
12. Phoenix 1.3 User's Guide, Pharsight Corporation.