CLINICAL STUDY PROTOCOL

Study CRO-PK-21-355 - Sponsor code 21CH-TAD08

Comparative bioavailability study of a new IBSA tadalafil 20 mg orodispersible film vs. Cialis® 20 mg film-coated tablet in healthy men under fed and fasting conditions

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

Test formulation:	IBSA tadalafil 20 mg orodispersible film, IBSA Institut Biochimique S.A., Switzerland
Reference formulation:	Cialis®, tadalafil 20 mg film-coated tablet, Eli Lilly Nederland B.V., Netherland
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
Investigator:	Milko Radicioni, MD - Principal Investigator CROSS Research S.A., Phase I Unit, Via F.A. Giorgioli 14 CH-6864 Arzo, Switzerland Phone: +41.91.64.04.450 Fax: +41.91.64.04.451 Email: clinic@croalliance.com
Development phase:	Phase I
Version and date:	Final version 1.0, 21OCT2021

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

This document comprises 63 pages

2 PROTOCOL APPROVAL

2.1 SPONSOR

IBSA Institut Biochimique S.A., Switzerland

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Carol Caverzasio, R&D Scientific Affairs Specialist

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Date Signature

Project Supervisor
Stefano Rovati, Sr. R&D Scientific Affairs Manager

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Drug Safety Manager
Gabriele Brunetti, Deputy European Qualified Person for Pharmacovigilance QPPV

21/10/2021 _____
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Representative
Giuseppe Mautone, Head of R&D Scientific Affairs

20/10/2021 _____
Date Signature

21/10/2021

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

21 OCT 2021 _____
Date

Signature

2.3 CRO

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Elena Gander, Clinical Project Leader

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Biometry Unit Representative
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3 STUDY SYNOPSIS

Title: Comparative bioavailability study of a new IBSA tadalafil 20 mg orodispersible film vs. Cialis® 20 mg film-coated tablet in healthy men under fed and fasting conditions
Protocol number: CRO-PK-21-355 - Sponsor code 21CH-TAD08
Clinical phase: Phase I
Study design: Single centre, single dose, open-label, randomised, 3-way cross-over, fed and fasting conditions, 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): IBSA tadalafil 20 mg orodispersible film (ODF), IBSA Institut Biochimique S.A., Switzerland Reference product (R): Cialis®, tadalafil 20 mg film-coated tablets, Eli Lilly Nederland B.V., Netherland
Dose regimen: A single dose of IBSA tadalafil 20 mg ODF under fed conditions, a single dose of IBSA tadalafil 20 mg ODF under fasting conditions and a single dose of Cialis® film-coated tablet under fed conditions will be administered to the study volunteers in three study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 12 days between the three consecutive administrations. The investigational products will be orally administered to the volunteers on Day 1 of each study period at 08:00±1 h as follows: ➢ T_{fed}: one IBSA tadalafil 20 mg ODF administered under fed conditions ➢ T_{fast}: one IBSA tadalafil 20 mg ODF administered under fasting conditions ➢ R_{fed}: one Cialis® 20 mg film-coated tablet administered under fed conditions
Objective: **Primary objective:** To compare the bioavailability of tadalafil in healthy male volunteers after single dose of the test product under fed conditions and the reference product under fed conditions. **Secondary objectives:** ➢ To compare the bioavailability of tadalafil in healthy male volunteers after single dose of the test product under fed and fasting conditions ➢ To describe the plasma pharmacokinetic parameters and profile of tadalafil after single dose of the test product under fed and fasting conditions and the reference product under fed conditions ➢ To collect safety and tolerability of the study treatments.
End-points: **Primary end-points:** ➢ To evaluate rate (C_{max} and t_{max}) and extent (AUC_{0-72h}) of tadalafil absorption in plasma after single dose of T and R under fed conditions **Secondary end-points:** ➢ To evaluate rate (C_{max} and t_{max}) and extent (AUC_{0-72h}) of tadalafil absorption in plasma after single dose of T under fed and fasting conditions ➢ To describe the plasma pharmacokinetic parameters and profile of tadalafil after single dose of T under fed and fasting conditions and R under fed conditions ➢ To collect safety data after single dose of T under fed and fasting conditions and R under fed conditions.
Study variables: **Primary variables:** ➢ C_{max}, t_{max} and AUC_{0-72h} of plasma tadalafil after single dose of T and R under fed conditions

STUDY SYNOPSIS (cont.)

Study variables (cont.):
Secondary variables:

- C_{max}, t_{max} and $AUC_{0\text{-}72h}$ of plasma tadalafil after single dose of T under fed and fasting conditions
- F_{rel}, $AUC_{0\text{-}8h}$ and, if feasible, $AUC_{0\text{-}\infty}$ and $t_{1/2}$ of plasma tadalafil

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

Analytics: Tadalafil concentrations will be determined in plasma samples at Anapharm Europe, S.L.U., Spain, using a fully validated LC-MS/MS method. Analyses will be performed in compliance with GCP regulations, following applicable GLP principles.

Sample size: Fifteen (15) healthy male volunteers will be enrolled in the study in order to have 12 completed subjects. Discontinued subjects will not be replaced up to a maximum of 3; if more than 3 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 explorative 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, 18-45 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

Exclusion criteria:

1. *Electrocardiogram 12-leads (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 (phosphodiesterase type 5 inhibitors) 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; history of vision or hearing problems related to drugs of the phosphodiesterase type 5 inhibitor pharmacological class; history of priapism; anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease); history of ophthalmologic diseases like non-arteritic anterior ischemic optic neuropathy or retinitis pigmentosa
6. *Medications*: medications, including over the counter medications and herbal remedies for 2 weeks before the start of the study. Nitrates will not be allowed for 2 weeks before screening.
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 [>2 drinks/day, 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 or Day -1
11. *Alcohol test*: positive alcohol breath test at Day -1
12. *Diet:* abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians

STUDY SYNOPSIS (cont.)

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 ➢ Drug screening test ➢ Adverse event 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
Visit 2	*Day -1*	➢ Alcohol breath test ➢ Drug screening test ➢ 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 2 Standardised dinner
Visit 3	*Days 1-2*	➢ Investigational product administration at 08:00±1h (for subjects under fed conditions, 30 min after start of breakfast) (only Day 1) ➢ Vital signs (blood pressure, heart rate) measurement at pre-dose (0), 4, 5 and 24 h post-dose ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0) and 20 min, 40 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12 and 24 h post-dose ➢ Adverse events and concomitant medications	Fasting overnight (fed and fasting subjects), for at least 10 h before the morning of Day 1 <u>Day 1</u> *Fed conditions*: standardised high-fat, high-caloric breakfast 30 min pre-dose to be completed within 30 min from start *Fasting conditions*: no breakfast All subjects (fed and fasting conditions) will be fasting for 5 h post-dose. Standardised lunch and dinner 5 and 12 h post-dose, respectively. <u>Day 2</u> Discharge from the Phase I Unit in the morning, after the 24 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

STUDY SYNOPSIS (cont.)

Schedule (cont.):			
	Day	**Procedures/Assessments**	**Notes**
Visit 4	*Day 3*	➢ Blood sample collection for pharmacokinetic analysis at 48 h post-dose ➢ Adverse events and concomitant medications	Ambulatory visits
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	
Wash-out	*At least 12 days*	➢ A wash-out interval of at least 12 days will elapse between the two administrations of Periods 1 and 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	*Days 1-2*	➢ As Visit 3	As Visit 3
Visit 8	*Day 3*	➢ As Visit 4	Ambulatory visits
Visit 9	*Day 4*	➢ As Visit 5	
Wash-out	*At least 12 days*	➢ A wash-out interval of at least 12 days will elapse between the two administrations of Periods 2 and 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	*Days 1-2*	➢ As Visit 3	As Visit 3
Visit 12	*Day 3*	➢ As Visit 4	Ambulatory visits
Visit 13	*Day 4*	➢ As Visit 5	

STUDY SYNOPSIS (cont.)

Final Visit/ETV	*Day 4 of period 3 or early termination visit 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 ➢ 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 normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions

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 2. 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 allocated to the treatment under fasting conditions will not take any food or drinks (except water) before investigational product administration, whereas the subjects allocated to the treatment under fed conditions will receive a high-fat high-caloric breakfast. The meal will be served 30 min pre-dose and should be completed within 30 min. Then all the subjects will remain fasted until 5 h post-dose. Standardised lunch and dinner will be served approximately 5 and 12 h post-dose.
Water will be allowed as desired, except for 1 h before and 1 h after investigational product administration. In order 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 (excluding the breakfast); any other coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit and 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, excluding breakfast.
During confinement, routine ambulant daily activities will be strongly recommended. For the 4 h following the administration, when not involved in study activities, the subjects will remain seated. They will not be allowed to lie down. 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.
Analysis sets:
Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics.
Safety set: all subjects who receive at least one dose of the investigational medicinal product. This analysis set will be used for the safety analyses.
Pharmacokinetic set 1: all enrolled subjects who fulfil the study protocol requirements in terms of T_{fed} and R_{fed} intake and have evaluable pharmacokinetic data readouts for the planned comparison of T_{fed} vs. R_{fed}, with no major deviations that may affect the pharmacokinetic results. This analysis set will be used for the statistical comparison between test and reference products administered under fed conditions.
Pharmacokinetic set 2: all enrolled subjects who fulfil the study protocol requirements in terms of T_{fed} and T_{fast} intake and have evaluable pharmacokinetic data readouts for the planned comparison of T_{fed} vs. T_{fast}, with no major deviations that may affect the pharmacokinetic results. This analysis set will be used for the statistical comparison statistical comparison between test product administered under fasting and fed conditions.

STUDY SYNOPSIS (cont.)

Pharmacokinetic analysis:
The pharmacokinetic analysis will be performed using Phoenix WinNonlin® version 6.3 (or higher) and SAS® version 9.3 (TS1M1) or higher. Tadalafil C_{max}, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}\infty}$ (if feasible) will be compared between T and R product administered under fed conditions (T_{fed} vs. R_{fed}) and separately between T product administered under fed and fasting conditions (T_{fed} vs. T_{fast}) 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 interval will be calculated for the point estimates (i.e., the T_{fed}/R_{fed} or T_{fed}/T_{fast} ratio of least square geometric means) of the PK parameters using the acceptance interval 80.00-125.00% as a reference. For the comparison between T_{fed} and T_{fast}, established criteria for the absence of a food effect are that the 90% confidence interval for the ratio of the geometric means of the parameters under consideration between fed and fasting conditions are within the 80.00-125.00% range. T_{max} will be compared between treatments separately (T_{fed} vs. R_{fed} and T_{fed} vs. T_{fast}) using the non-parametric Wilcoxon signed-rank test.
Demography and safety analysis:
The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 TS1M1 (or higher).

Timing:
EC meeting: NOV21; planned clinical phase: FEB2022

4 STUDY SCHEDULE

ACTIVITIES	Screening	PERIOD 1, 2, 3 (wash-out≥12 days)				V14, Final visit/ETV[10]
Visit	**V1**	**V2, V6, V10**	**V3, V7, V11**	**V4, V8, V12**	**V5, V9, V13**	
	Day -21/-2	**Day -1**	**Days 1-2**	**Day 3**	**Day 4**	**Day 4[11]**
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					
Body Weight	x					x
Laboratory analysis	x					x
Virology	x					
Drug screening test	x	x				
Blood pressure and heart rate	x		x[6]		x	x[13]
ECG	x					x
Alcohol breath test		x				
Inclusion/exclusion criteria	x	x[1]				
Subject eligibility	x	x[1]				
Enrolment and randomisation		x[1]				
Confinement[2]		x	x			
Discharge			x[2]			
Investigational product administration			x[5]			
Blood sampling			x[7]	x[8]	x[9]	
Standardised meals		x[3]	x[4]			
Adverse event monitoring[11]	x	x	x	x	x	x

1. *Only at Visit 2*
2. *Confinement from Day -1 (evening) up to the morning of Day 2*
3. *Standardised low-fat dinner*
4. *Only for fed subjects, high-fat high-caloric breakfast; for all subjects, standardised lunch and dinner at approximately 5 and 12 h post-dose (Day 1)*
5. *On Day 1 at 8:00 ± 1 h (for fed subjects, 30 min after start of high-caloric, high-fat breakfast)*
6. *At pre-dose (0), 4, 5 and 24 h post-dose*
7. *At pre-dose (0), 20 min, 40 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12 and 24 h post-dose*
8. *At 48 h post-dose*
9. *At 72 h post-dose*
10. *Early termination visit (ETV) in case of premature discontinuation*
11. *Final visit on Day 4 of Period 3 after the 72h post-dose blood sampling and safety assessments*
12. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*
13. *At ETV only*

5 TABLE OF CONTENTS

5.1 TABLES

6 LIST OF ABBREVIATIONS

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_{0-8h}	Area under the concentration-time curve from administration to 8 h post-dose
AUC_{0-72h}	Area under the concentration-time curve from administration to 72 h post-dose
$AUC_{0-\infty}$	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
cGMP	Cyclic guanosine monophosphate
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CPL	Clinical Project Leader
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
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
EMA	European Medicines Agency
ETV	Early Termination Visit
F_{rel}	Relative bioavailability
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
IMP	Investigational Medicinal Product
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
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
PDE	Phosphodiesterase type 5
PDE5	Guanosine monophosphate (cGMP)-specific phosphodiesterase type 5
PE	Point Estimate
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R	Reference
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
T_{fed}	Test treatment under fed conditions
T_{fast}	Test treatment under fast conditions
$t_{1/2}$	Half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to achieve C_{max}
TMF	Trial Master File
USDA	United States Department of Agriculture
WHODDE	World Health Organisation Drug Dictionary Enhanced

7 INTRODUCTION

7.1 Background

Penile erection is the end result of smooth muscle relaxation in the penis and includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism. Erectile dysfunction is defined as the persistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual performance.

Tadalafil is a well-known active substance used for the treatment of erectile dysfunction and benign prostatic hyperplasia in adult males. Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). PDE5 is a regulator of vascular smooth muscle contraction in all smooth muscle districts and especially in penis. When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in the vascular smooth muscle relaxation, vasodilation and inflow of blood into the penile tissues, thereby producing an erection (1).

PDE5 inhibitors are currently the first-line therapy for erectile dysfunction and the three potent selective PDE5 inhibitors sildenafil, tadalafil and vardenafil were approved by the European Medicines Agency (EMA) and by more than 100 national competent authorities and are currently on the market for the treatment of erectile dysfunction (2).

7.2 Pharmacokinetic (PK) of tadalafil

Tadalafil is rapidly absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute oral bioavailability of tadalafil following oral dosing has not been determined (1).

The mean volume of distribution is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects (1).

Tadalafil is predominantly metabolised by the cytochrome P450 hemeprotein. The major circulating metabolite is the methyl catechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations (1).

The mean oral clearance for tadalafil is 2.5 L/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose) (1).

7.3 Phase I clinical studies of IBSA tadalafil 20 mg orodispersible film (ODF)

Initially, the Sponsor conducted a bioavailability study (Sponsor's code: 17CDN-TAD03, 3) to preliminarily evaluate the PK profile of a formulation of tadalafil 20 mg ODF administered

in fasting conditions as compared to the reference product Cialis® 20 mg tablets (Eli Lilly and Company Ltd., USA). This study involved 15 male volunteers aged 18-50 (14 completed the study and were considered for the PK analysis) and did not show similar bioavailability between the two formulations, leading IBSA to modify and ameliorate the ODF formulation. Subsequently, the Sponsor conducted another bioavailability study (Sponsor's code: 18CDN-TAD13, 4) to compare the new tadalafil 20 mg ODF formulation and Cialis® 20 mg tablets (Eli Lilly and Company Ltd., USA) when administered to healthy subjects under fasting conditions. The study involved 15 male volunteers, aged 18-50. The PK results demonstrated that the IBSA tadalafil 20 mg ODF and Cialis® 20 mg tablet could have been considered bioequivalent with respect to rate and extent of absorption when administered under fasting conditions (based on the content of the current edition of EMA Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, 20JAN10, 7).

A further pilot study was conducted in 12 healthy male adults, 18-50 years old, to evaluate the effect of food on the PK of tadalafil 20 mg ODF (Sponsor's code:19CDN-TAD07, 5). The rate and extent of absorption of tadalafil were measured and compared after a single dose of test product administered under fasting conditions or following a high-fat meal. The peak of concentration was lower (decreased approximately by 23%) and t_{max} delayed (approximately 1 hour) when tadalafil ODF was taken under fed conditions, while the food did not significantly affect the extent of exposure.

The results of the last PK study led IBSA to further ameliorate the tadalafil ODF formulation so as to reach a similar bioavailability, when assumed in fed condition, to the originator product Cialis®.

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

7.4 Safety

Generally, the administration of IBSA tadalafil 20 mg ODF to healthy subjects in previous clinical studies was safe and well tolerated.

In the first bioavailability study detailed in § 7.3 (3), no serious adverse events (SAEs) and no deaths were reported for any of the subjects enrolled. No subject was withdrawn by the Investigator for safety reasons. A total of 25 treatment-emergent AEs (TEAEs) were reported in 10 (67%) of the 15 subjects participating in this study. Of these events, 7 occurred after administration of tadalafil 20 mg ODF and 7 TEAEs occurred after administration of the Reference. Most of the TEAEs were considered related to drug administration (23/25; 92%). The TEAEs experienced during the study were deemed mild (16/25; 64%) and moderate (9/25; 36%) in intensity. None of the subjects experienced a severe TEAE during the study. The TEAE experienced most commonly in this study was headache. Other TEAEs experienced less frequently included nausea and back pain. Generally, the subjects showed laboratory values within reference range in all treatment groups. However, one subject (7%) in this study showed an abnormal urinalysis result (blood in urine), which was considered clinically significant by the Investigator and reported as a mild TEAE: red blood cells urine positive. The event was ongoing at the end of the study. Furthermore, there were no clinically significant abnormalities in the vital signs of the subjects in this study and all physical examinations were considered normal.

In the second bioavailability study detailed in § 7.3 (4), no SAEs occurred, and no subject discontinued the study due to safety reasons. A total of 27 TEAEs were experienced by 13 of the 15 subjects (87%) who participated in this study, of which 11 occurred after administration of tadalafil 20 mg ODF. Most TEAEs experienced during the study were considered drug-related (22/27; 82%), with an overall severity of mild (93%) and moderate (7%). The most common TEAEs experienced after administration of tadalafil 20 mg ODF were back pain (20%), headache (20%), myalgia (13%), pain in extremity (7%), dizziness and vessel puncture site erythema (7%).
All TEAEs experienced during the study resolved within the end of the study. No significant effects of treatment on vital signs, physical examination and laboratory parameters were observed.

In the previous pilot study detailed in § 7.3 (5), no serious AEs occurred, and no subject discontinued the study due to safety reasons.
All TEAEs reported in this study were deemed related to drug administration, with a severity mild (88%) and moderate (12%). A total of 17 TEAEs were experienced by 7 of the 12 subjects (58%), of which 9 occurred after administration of treatment under fed conditions and 8 under fasting conditions. The most common TEAE was back pain, reported by 2 subjects (17%) after administration of each treatment. Other TEAEs experienced less frequently included limb discomfort, headache, sciatica and euphoric mood, reported by 1 subject (8%) after administration of each treatment. The remaining TEAEs were arthralgia, pain in extremity and feeling hot (1 subject, 8%), hypoesthesia and nausea (1 subject, 8%).
All TEAEs resolved within the end of the study. No significant effects of treatment on vital signs, physical examination and laboratory parameters were observed.

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

7.5 Rationale

The Sponsor, IBSA Institut Biochimique S.A., has developed a new ODF containing tadalafil, to provide an easy to take and rapidly dissolvable alternative to the marketed products for erectile dysfunction treatment.

As reported in tadalafil bioequivalence guidance (9) and observed in the previous mentioned clinical study (5), the pharmaceutical formulation (e.g., particle size and excipients) could affect the pharmacokinetic of tadalafil when administered under fed conditions.

For the European market registration of the IBSA tadalafil 20 mg ODF formulation, the Sponsor must show similar bioavailability of its product to the European marketed originator Cialis® 20 mg film-coated tablet in both fasting and fed conditions. With this in mind and in order to further develop the European project registration of the product, IBSA will conduct an additional comparative bioavailability study on the new ODF formulation when administered in both fasting and fed condition compared to Cialis® 20 mg film-coated tablet administered in fed condition. Therefore, the objective of the present single dose, randomised, 3-way cross over pilot bioavailability study is to evaluate the bioavailability of tadalafil in healthy male volunteers after a single dose of tadalafil 20 mg ODF under fed and fasting

conditions, vs. Cialis® 20 mg tablet under fed conditions. Tadalafil bioavailability will be compared in healthy male volunteers in terms of rate (C_{max} and t_{max}) and extent ($AUC_{0\text{-}72h}$) of absorption.

7.6 Risks and benefits

On the basis of tadalafil safety profile, no potential risks are foreseen for the subjects enrolled in the present study.

According to the safety data of the previous Phase I studies in healthy men (3, 4, 5), the reported TEAEs at frequencies >10% were, in order of decreasing frequency, back pain, headache and myalgia.

Blood sampling with cannula insertion may cause minor discomfort. The risks associated with blood draws include pain, bleeding and bruising.

No potential benefits are foreseen to subjects participating in this study.

8 STUDY OBJECTIVES

8.1 Primary objective

The objective of the study is to compare the bioavailability of tadalafil in healthy male volunteers after single dose of the test product (T) under fed conditions and the reference product (R) under fed conditions.

8.2 Secondary objectives

Secondary objectives of the study are the following:

- To compare the bioavailability of tadalafil in healthy male volunteers after single dose of the test product under fed and fasting conditions
- To describe the plasma pharmacokinetic parameters and profile of tadalafil after single dose of the test product under fed and fasting conditions and the reference product under fed conditions
- To collect safety and tolerability of the study treatments.

8.3 Primary end-points

- To evaluate rate (C_{max} and t_{max}) and extent ($AUC_{0\text{-}72h}$) of tadalafil absorption in plasma after single dose of T and R under fed conditions.

8.4 Secondary end-points

- To evaluate rate (C_{max} and t_{max}) and extent ($AUC_{0\text{-}72h}$) of tadalafil absorption in plasma after single dose of T under fed and fasting conditions
- To describe the plasma PK parameters and profile of tadalafil after single dose of T under fed and fasting conditions and R under fed conditions
- To collect safety data after single dose of T under fed and fasting conditions and R under fed conditions.

9 CLINICAL SUPPLIES

9.1 Treatment

Each subject will receive each of three treatments (T_{fed}, T_{fast} and R_{fed}) in three consecutive study periods.

9.1.1 Description of products

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

9.1.1.1 Test product

IMP	IBSA tadalafil 20 mg ODF
Active substance	Tadalafil
Distributor	IBSA Institut Biochimique S.A., Switzerland
Manufacturer (active substance)	Pharmaceutical Works Polpharma S.A., Poland
Manufacturer (finished product)	IBSA Farmaceutici Italia Srl, Italy
Pharmaceutical form	Orodispersible film (ODF)
Dose	20 mg
Administration route	Oral

The Test product will be administered under fed conditions (T_{fed}) and under fasting conditions (T_{fast}), as detailed in § 9.1.3.

9.1.1.2 Reference product

IMP	Cialis® 20 mg film-coated tablet
Distributor	Eli Lilly Nederland B.V., Netherland
Pharmaceutical form	Film-coated tablet
Dose	20 mg
Administration route	Oral

The Reference product will be obtained from the Italian market. It will be administered under fed conditions (R_{fed}) only, as detailed in § 9.1.3.

9.1.2 Dose regimen

For each subject, a single dose of IBSA tadalafil 20 mg ODF under fed conditions (T_{fed}), a single dose of IBSA tadalafil 20 mg ODF under fasting conditions (T_{fast}) and a single dose of Cialis® film-coated tablet under fed conditions (R_{fed}) will be administered in three study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 12 days between the three consecutive administrations.

9.1.3 Route and method of administration

The IMPs will be orally administered to the volunteers on Day 1 of each study period at 08:00±1 h as follows:

- T_{fed}: one IBSA tadalafil 20 mg ODF administered under fed conditions
- T_{fast}: one IBSA tadalafil 20 mg ODF administered under fasting conditions
- R_{fed}: one Cialis® 20 mg film-coated tablet administered under fed conditions.

Before the administration of T, the subject will wet the mouth with 20 mL of still mineral water. Then, the Investigator or deputy will take the film out of the sachet and place it directly on the subject's tongue. The Investigator will wear gloves during the administration procedure.
The film will dissolve rapidly. Subjects will let the ODF completely dissolve in their mouth. The film must not be swallowed whole and must not be chewed or broken. The subject will be allowed to swallow saliva as the film dissolves in the mouth.
In details, once the subject feels that the film has completely dissolved, he 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 mouth will be checked by the Investigator at two and three minutes.
If, upon inspection at two or three minutes, the film is already dissolved, the time of mouth check will be recorded as time of dissolution.
If the film 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_{fed} and T_{fast} treatments' administrations, the exact date and time of ODF administration (defined as the time at which the ODF is placed on the subject's tongue by the Investigator or deputy) and the time of complete dissolution of the ODF (no residues present at inspection of the oral cavity by the Investigator or deputy) will be recorded. Film 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 R 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. Reference product administration date and time will be recorded as well.

The subjects receiving the treatments under fed conditions (T_{fed} and R_{fed}) will take the IMP 30 min after having started to eat a high-fat and high-caloric breakfast. Breakfast must be completed within 30 minutes from start. The subjects receiving T_{fast} will take it under prolonged fasting conditions (from at least 10 h pre-dose).

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

9.1.4 Investigational product distribution

The IMPs will be administered by the Investigator or by his/her 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 15 individual subject's kits and 5 reserve kits. Each kit will include 2 sachets containing 1 IBSA tadalafil 20 mg ODF each and 1 blister with 2 Cialis® 20 mg film-coated tablets (the second tablet should not be administered, and for this reason will be covered). Primary packaging of tadalafil 20 mg ODF will be a PET/Aluminium Foil/PE Peel laminate sachet.

The formulation 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; 10) as follows:

a. Name, address and telephone number of the Sponsor, contract research organisation 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. Only for the individual subject's kits, 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 (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)
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

The 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 pharmacist 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 test IMP provided by the Sponsor will either be destroyed on site (upon written authorisation) 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, fed and fasting conditions, pilot bioavailability study.

10.2 Discussion of design

The study has been designed taking into consideration the following guidelines: Guidance on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr **, 20 January 2010 (7), Guideline on investigation of drug interactions, CPMP/EWP/560/95/Rev. 1 Corr. 2**, 21 June 2012 (8) and Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance, EMA/CHMP/315234/2014/Rev.1, 25 January 2018 (9).

The investigation will compare tadalafil pharmacokinetic parameters after administration of tadalafil 20 mg ODF under fed and fasting conditions, and after administration of tadalafil 20 mg ODF under fed conditions vs. Cialis® 20 mg tablet under fed conditions.

Each randomised subject will be allocated to one sequence of treatments according to a computer-generated randomisation list (see § 14.1) and to the 3-way cross-over design.

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

The dose of 20 mg of tadalafil was chosen on the basis of the clinical practice, the recommended dose regimen of 2.5-20 mg and according to the specific guidance, which specifies that the highest strength should be used.

An open-label design is used since the primary end-point of the study is based on objective measurements of tadalafil in blood. 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 the tadalafil and the results of the previous Phase I studies (4, 5).

Wash-out interval between subsequent administrations is based on tadalafil half-life.

11 STUDY POPULATION

11.1 Target population

The study population will include 15 healthy men, aged 18-45 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, 18-45 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

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 (PDE5 inhibitors) 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; history of vision or hearing problems related to drugs of the PDE5 inhibitor pharmacological class; history of priapism; anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease); history of ophthalmologic diseases like non-arteritic anterior ischemic optic neuropathy or retinitis pigmentosa
6. *Medications*: medications, including over the counter (OTC) medications and herbal remedies for 2 weeks before the start of the study. Nitrates will not be allowed for 2 weeks before screening.

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 [>2 drinks/day, defined according to the USDA Dietary Guidelines 2020-2025 (11)], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. *Drug test*: positive result at the drug test at screening or Day-1
11. *Alcohol test*: positive alcohol breath test at Day -1
12. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians

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. In particular, organic nitrates that are absolute contraindication to the use of PDE5 inhibitors will be strictly forbidden for 2 weeks before the start of the study.

Paracetamol will be allowed as therapeutic countermeasure for 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 14 visits.

The study protocol foresees 3 periods separated by wash-out intervals of at least 12 days. Minimum study duration will be 30 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
  - Visit 2: Day -1
- **Interventional phase**
  - Visit 3: Days 1-2
  - Visits 4 and 5: Days 3-4 (ambulatory visits)
  - Wash-out interval of at least 12 days
  - Visit 6: Day -1
  - Visit 7: Days 1-2
  - Visits 8 and 9: Days 3-4 (ambulatory visits)
  - Wash-out interval of at least 12 days
  - Visit 10: Day -1
  - Visit 11: Days 1-2
  - Visit 12 and 13: Days 3-4 (ambulatory visits)
- **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 (blood pressure, heart rate) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis, virology ➢ 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
Visit 2	*Day -1*	➢ Alcohol breath test ➢ Drug screening test ➢ 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 2 Standardised dinner
Visit 3	*Days 1-2*	➢ IMP administration at 08:00±1h (for subjects under fed conditions, 30 min after start of breakfast) (only Day 1) ➢ Vital signs (blood pressure, heart rate) measurement at pre-dose (0), 4, 5 and 24 h post-dose ➢ Blood sample collection for PK analysis at: pre-dose (0) and 20 min, 40 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12 and 24 h post-dose ➢ AEs and concomitant medications	Fasting overnight (fed and fasting subjects), for at least 10 h before the morning of Day 1 <u>Day 1</u> *Fed conditions*: standardised high-fat, high-caloric breakfast 30 min pre-dose to be completed within 30 min from start *Fasting conditions*: no breakfast All subjects (fed and fasting conditions) will be fasting for 5 h post-dose. Standardised lunch and dinner approximately 5 and 12 h post-dose, respectively. <u>Day 2</u> Discharge from the Phase I Unit in the morning, after the 24 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
Visit 4	*Day 3*	➢ Blood sample collection for PK analysis at 48 h post-dose ➢ AEs and concomitant medications	Ambulatory visits
Visit 5	*Day 4*	➢ Vital signs (blood pressure, heart rate) measurement at 72 h post-dose ➢ Blood sample collection for PK analysis at 72 h post-dose ➢ AEs and concomitant medications	
Wash-out	*At least 12 days*	➢ A wash-out interval of at least 12 days will elapse between the two administrations of Periods 1 and 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	*Days 1-2*	➢ As Visit 3	As Visit 3
Visit 8	*Day 3*	➢ As Visit 4	Ambulatory visits
Visit 9	*Day 4*	➢ As Visit 5	
Wash-out	*At least 12 days*	➢ A wash-out interval of at least 12 days will elapse between the two administrations of Periods 2 and 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	*Days 1-2*	➢ As Visit 3	As Visit 3
Visit 12	*Day 3*	➢ As Visit 4	Ambulatory visits
Visit 13	*Day 4*	➢ 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 (blood pressure, heart rate) (ETV only) ➢ ECG recording ➢ Laboratory analyses as at screening, with the exception of virology ➢ 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 normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse 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 allocated to the treatment under fasting conditions will not take any food or drinks (except water) before IMP administration, whereas the subjects allocated to the treatment under fed conditions will receive a high-fat high-caloric breakfast (see § 12.2.1). The meal will be served 30 min pre-dose and should be completed within 30 min. Then all the subjects will remain fasted until 5 h post-dose. Standardised lunch and dinner will be served approximately 5 and 12 h post-dose.

Water will be allowed as desired, except for 1 h before and 1 h after IMP administration. In order 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 (excluding breakfast); any other coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit and 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, excluding the breakfast.

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

12.2.1 Standardized high-fat and high-caloric breakfast

As reported above, on Day 1 of each study period, subjects randomised to the treatments under fed conditions will start to eat a high-fat and high-caloric breakfast 30 min pre-dose and will be instructed to complete their meal within 30 min from start, before the IMP administration.

Breakfast caloric content will be approximately 1000 kilocalories (kcal) and fat content will be approximately 60% of the total caloric content. The standardized breakfast, which is detailed in the table below, will provide approximately 15%, 25% and 60% of the calories from proteins, carbohydrates and fats, respectively.

Table 12.2.1.1 High-caloric and high-fat breakfast composition

Food	Amount (g)	Fats (g)	Carbohydrates (g)	Proteins (g)	kcal
Whole milk	250	8	12	8	160
Two fried eggs	140	14	1	13	180
Butter	30	25	0	0	227
Two strips of bacon	50	12	0	8	138
Two slices of toast	50	4	35	4	150
Olive oil white bread	40	2	20	4	100

12.2.2 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 2.

During confinement, the subjects will not take any food or drinks, except water, apart from the standardised meals. For the 4 h following the administration, when not involved in study activities, the subjects will remain seated. They will not be allowed to lie down.

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

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 blood pressure (BP) and heart rate (HR) will be measured by the Investigator or deputy after 5 min at rest in sitting position at:

- Screening visit
- On Days 1-2 and 4 at pre-dose (0), 4, 5, 24 and 72 h post-dose of each study period
- 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 and on Day -1 of each study period.

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 (6 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 20 min, 40 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 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 40 minutes before IMP administration
20 min (0.33 h)	± 1 min
40 min (0.67 h)	± 2 min
1, 1.5 h	± 3 min
2, 2.5, 3, 3.5, 4 h	± 5 min
4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24 h	± 10 min
48 h	± 30 min
72 h	± 60 min

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution 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 4 mL will be collected from the catheter and transferred with a syringe into EDTA K_2 tubes.

After collection, blood samples will be stored on ice for a maximum of 45 min. Then the samples will be centrifuged at 4° C (± 4°C) for at least 10 min at 1900 g (± 38 g) to obtain plasma. Each plasma sample will be immediately divided into three aliquots, P1 (0.5 mL), P2 (0.5 mL), P3 (the remaining amount, if feasible), in pre-labelled polypropylene tubes, and stored frozen at ≤ -20° C until analyses. The time between the end of centrifugation and plasma aliquot storage cannot exceed 195 min.

If any clinical assessment, such as vital signs measurement or ECG recording, is foreseen at the same time-point of 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 all 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 tadalafil in plasma samples will be determined at Anapharm Europe, S.L.U., Spain, 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 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-21-355 - Sponsor code 21CH-TAD08
Subject number	001 to 015
Tube identification	P1/P2/P3
Study period	1/2/3
Scheduled sampling time	as h; see § 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, P2 and P3 will be stored in separate freezers.

All aliquots P1, packed in sufficient solid CO_2, will be shipped by an authorised courier from CROSS Research S.A. Phase I Unit, Switzerland, to the analytical laboratory, Anapharm Europe, S.L.U., Spain. All aliquots will remain stored at the analytical laboratory for 3 months after the finalisation of the bioanalytical report.
After that period, the Sponsor will decide to either destroy or return or store aliquots for an extended period of time 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
- destroyed at an authorised site, or
- transferred to the Sponsor upon written request, or
- stored at CROSS Research S.A., for a maximum time of 5 years
- 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:

66 samples x 6 mL = 396 mL

In total 421 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 the SAS® version 9.3 (TS1M1) (12) or higher (the actual version will be stated in the final report). The randomisation list will be supplied to the study site before study start. 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 ($T_{fed}/T_{fast}/R_{fed}$; $T_{fast}/T_{fed}/R_{fed}$; $R_{fed}/T_{fed}/T_{fast}$; $R_{fed}/T_{fast}/T_{fed}$; $T_{fed}/R_{fed}/T_{fast}$; $T_{fast}/R_{fed}/T_{fed}$) 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. Analytical laboratory will be in blind conditions.

15 EVALUATION PARAMETERS

15.1 Study variables

15.1.1 Primary variables

- C_{max}, t_{max} and $AUC_{0\text{-}72h}$ of plasma tadalafil after single dose of T and R under fed conditions

15.1.2 Secondary variables

- C_{max}, t_{max} and $AUC_{0\text{-}72h}$ of plasma tadalafil after single dose of T under fed and fast conditions
- F_{rel}, $AUC_{0\text{-}8h}$ and, if feasible, $AUC_{0\text{-}\infty}$ and $t_{1/2}$ of plasma tadalafil
- 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 tadalafil, using the validated software Phoenix WinNonlin® version 6.3 (13) 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 $\ln 2/\lambda_z$
$AUC_{0\text{-}t}$:	Area under the concentration-time curve from administration to the last observed concentration time t, calculated with the linear trapezoidal method
$AUC_{0\text{-}8h}$:	Area under the concentration-time curve from administration to 8 h post-dose, calculated with the linear trapezoidal method
$AUC_{0\text{-}72h}$:	Area under the concentration-time curve from administration to 72 h post-dose, calculated with the linear trapezoidal method
$AUC_{0\text{-}\infty}$:	Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0\text{-}t} + C_t/\lambda_z$, 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_{0-72h} (Test)/AUC_{0-72h} (Reference) for T_{fed} vs. R_{fed} and T_{fed} vs. T_{fast}

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 statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (12) 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 (13) or higher and SAS® version 9.3 (TS1M1) or higher (12).

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 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 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:

- Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics.
- Safety set: all subjects who receive at least one dose of IMP. This analysis set will be used for the safety analyses.
- PK set 1: all enrolled subjects who fulfil the study protocol requirements in terms of T_{fed} and R_{fed} intake and have evaluable pharmacokinetic data readouts for the planned comparison of T_{fed} vs. R_{fed}, with no major deviations that may affect the pharmacokinetic results. This analysis set will be used for the statistical comparison between test and reference products administered under fed conditions.
- PK set 2: all enrolled subjects who fulfil the study protocol requirements in terms of T_{fed} and T_{fast} intake and have evaluable pharmacokinetic data readouts for the planned comparison of T_{fed} vs. T_{fast}, with no major deviations that may affect the pharmacokinetic results. This analysis set will be used for the statistical comparison statistical comparison between test product administered under fasting and fed 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

- subjects with lack of any measurable concentrations or only very low plasma concentrations for R_{fed}. A subject is considered to have very low plasma concentrations if his AUC is less than 5% of the R_{fed} route geometric mean AUC (which should be calculated without inclusion of data from the outlying subject)
- 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_{0-72h} covers less than 80% of the $AUC_{0-\infty}$.

16.2 Sample size and power considerations

Fifteen (15) healthy male volunteers will be enrolled in the study in order to have 12 completed subjects. Discontinued subjects will not be replaced up to a maximum of 3; if more than 3 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 explorative purposes of this 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 film dissolution time

For T_{fed} and T_{fast} treatments' administrations, the date and time of film placement and of film dissolution will be listed. Reference administration times will be listed as well. For all the three treatments, the occurrence of accidental chewing and/or breaking and/or swallowing will be listed. Administration time is defined as the time the film is placed on the subject's tongue for T_{fed} and T_{fast} 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).

16.6 Analysis of PK parameters

16.6.1 Statistical comparison of PK parameters

According to the current European Guideline on the Investigation of Bioequivalence (7) and European Guideline on Tadalafil film-coated tablets (9), C_{max}, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}\infty}$ (if feasible) will be compared between test and reference product administered under fed conditions (T_{fed} vs. R_{fed}) and separately between test product administered under fed and fasting conditions (T_{fed} vs. T_{fast}) 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 interval (CI) will be calculated for the point estimates (PE, i.e., the T_{fed}/R_{fed} or T_{fed}/T_{fast} ratio of least square geometric means) of the PK parameters using the acceptance interval 80.00-125.00% as a reference.

For the comparison between T_{fed} and T_{fast}, established criteria for the absence of a food effect are that the 90% CI for the ratio of the geometric means of the parameters under consideration between fed and fasting conditions are within the 80.00-125.00% range.

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

16.7 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 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 Investigator's Brochure (IB) (6) for the Test product and of the SmPC for the Reference product (1).

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 product

- **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 and SmPC as a reference.

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), relevant medical history and concomitant medications taken during the study, when allowed and if any;
- 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, if code broken – when applicable;
- detailed at best the circumstances leading to SAE occurrence and, in case of unblinding, detailed the reason for the code to be broken;
- Specific treatment of the SAE;
- Outcome;
- Investigator: name, address, phone number.

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

The target population which the protocol is referred to is of male patients.
The metabolism of tadalafil and its characteristics are considered limited to the target male organs, with no meaningful implications addressing the intercourse on female partners.
Therefore, this section is NA and no pregnancy reports will be collected or managed, being out of the purposes and design of the protocol.

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 legibility, 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 have to 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., 21CH-TAD08), 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 100% sight verification 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 detailed in a monitoring plan based on IBSA risk assessment, Risk Based Monitoring Plan and CROSS Research risk evaluation.

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

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

The Investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorised individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the Sponsor could perform some quality control activities to verify the compliance with the study procedures and the ICH-GCP 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 ALCOAC principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete).

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 of the Sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the Sponsor.

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 Sponsors, 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 authorised 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 and regulatory authorities. 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 jeopardising their further course of medical treatment
- the existence of a subject insurance cover and obligations following from this cover

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

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).

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 authorised 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
- **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 3; if more than 3 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 have to 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 and SmPC relative to the investigational 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 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).

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 authorisation 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 in order 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
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Sponsor Representatives
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Carol Caverzasio, R&D Scientific Affairs Specialist
Gabriele Brunetti, Deputy European Qualified Person for Pharmacovigilance QPPV
Giuseppe Mautone, Head of R&D Scientific Affairs

Medical Expert
Gabriele Brunetti, Deputy European Qualified Person for Pharmacovigilance 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
Phone: +41.91.64.04.450
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Email: clinic@croalliance.com

Principal Investigator
Milko Radicioni, MD

22.3 Drug assay

Anapharm Europe, S.L.U., Encuny 22, 2nd floor, 08038 Barcelona, Spain
Phone: +34.93.223.8636
Email: cjimenez@anapharmbioanalytics.com

Analytics representative
Cintia Jiménez, Laboratory Management

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

22.4 Centralized clinical laboratory

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22.5 Coordination, data analysis & reporting

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22.6 Monitoring

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23 REFERENCES

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