CLINICAL STUDY PROTOCOL

Study CRO-PK-20-346 - Sponsor code 20CH-SDF10

Comparative bioavailability study of Sildenafil 100 mg oral film vs. Viagra® 100 mg film-coated tablet administered to healthy men under fed conditions

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

Test product:	Sildenafil IBSA 100 mg oral film (OF), IBSA Institut Biochimique S.A., Switzerland
Reference product:	Viagra®, sildenafil 100 mg film-coated tablet, Pfizer Laboratories Div. Pfizer Inc. NY, US
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 3.0, 10MAY2021

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

VERSIONS' HISTORY

Version	Date	Description of Changes
1.0	24JUN20	Original document
2.0	28SEP20	As stated in § 6.4 "Rationale" of this clinical study protocol (CSP), the results of this study will be used for the Sildenafil oral film registration procedure in the US. The statistical analysis for the comparison of the pharmacokinetic parameters between treatments will be performed according to the recommendations of the current FDA guidelines for bioavailability and bioequivalence studies. For this reason, the study results will not be considered as exploratory. Also, an additional treatment, i.e. Test product administered with water (Test treatment 2), has been added and the study has changed from a 2-way to a 3-way cross-over design. Accordingly, the following changes to the CSP were made: ➢ The terms "pilot" and "exploratory" were removed from the study title, subtitle and text, as applicable. ➢ The number of subjects planned to be enrolled in the study has been increased. ➢ A third study period and a third treatment (i.e. Test product administered with water) have been added. ➢ The statistical analysis text has been slightly modified. ➢ The study "Sample size" text has been reformulated. ➢ Two additional PK sets for PK analysis have been added and reasons for exclusion from PK analysis modified accordingly. In addition: ➢ Reference to the recently issued *FDA Guidance for Industry: Compliance Policy for the Quantity of Bioavailability and Bioequivalence*

		Samples Retained Under 21 CFR 320.38(c) (August 2020) has been added. ➢ The name of the analytical laboratory has been corrected in the text. ➢ Considering the additional blood volume to be collected in Period 3, for each sampling 9 mL (and not 10 mL) of blood will be collected. In this way, the volume of blood withdrawn from each subject during the study will not exceed a normal blood donation. ➢ Drug administration and film dissolution time analysis has been added. ➢ Storage conditions were better detailed. ➢ MPV, Yeast and Trichomonas analyses added in par. 7.2 because routinely performed as part of the clinical laboratory assays ➢ A few typos were corrected.
3.0	10MAY2021	The Clinical Study Protocol (CSP) has been modified implementing the changes introduced by the CSP Amendment Nr. 2, Final version 1.0, 21APR21. Consequently, the following paragraphs have been modified: ➢ § 12.3.2 "Analytics" ➢ § 12.3.3.2 "Samples storage and transport" ➢ § 21.3 "Drug assay". This was done to introduce the additional analytical laboratory Syneos Health Clinique Inc., Canada. § 2.1 and § 21.1 have been also modified updating Sponsor representatives' roles.

2 PROTOCOL APPROVAL

2.1 SPONSOR

IBSA Institut Biochimique S.A., Switzerland

Project Leader
Carol Caverzasio, MSc, R&D Scientific Affairs Specialist

27MAY2021 _____
Date

_____
Signature

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

27 MAY 2021 _____
Date

_____
Signature

Drug Safety Manager
Chiara Godina, Qualified Person for Pharmacovigilance

26 May 2021 _____
Date

_____
Signature

Representative
Giuseppe Mautone, Head of R&D Scientific Affairs

28/MAY/2021 _____
Date

_____
Signature

2.2 INVESTIGATOR

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

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

10 MAY 2021 _____ _____
Date Signature

2.3 CRO

CROSS Research S.A., Switzerland

Coordination
Elena Gander, Clinical Research Associate and Clinical Trial Assistant

10MAY2021 — Elena Gander
Date — Signature

Medical Writing Team Representative
Chiara Leuratti, Clinical Projects Unit Head

10MAY 2021 — Chiara Leuratti
Date — Signature

Biometry Unit Representative
Alessandra Gentili, Biometry Manager, Unit Head

10MAY 2021 — Alessandra Gentili
Date — Signature

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

10 MAY 2021 — Mario Corrado
Date — Signature

3 STUDY SYNOPSIS

Title: Comparative bioavailability study of Sildenafil 100 mg oral film vs. Viagra® 100 mg film-coated tablet administered to healthy men under fed conditions
Protocol number: CRO-PK-20-346 - Sponsor code 20CH-SDF10
Clinical phase: Phase I
Study design: Single centre, single dose, randomised, open-label, 3-way cross-over, fed conditions, bioavailability study
Planned nr. of centres / countries: 1/Switzerland
Investigator and centre: *Principal Investigator*: Milko Radicioni, MD; *Centre*: CROSS Research Phase I Unit; Via F. A. Giorgioli 14, CH-6864 Arzo, Switzerland
Investigational products: Test product: Sildenafil IBSA 100 mg oral film (OF), IBSA Institut Biochimique S.A., Switzerland Test treatment 1 (T1): One Test product OF administered under fed conditions without water Test treatment 2 (T2) One Test product OF administered under fed conditions with water Reference product: Viagra®, sildenafil 100 mg film-coated tablet, Pfizer Laboratories Div. Pfizer Inc. NY, US Reference treatment (R): One Reference product tablet administered under fed conditions with water
Dose regimen: A single dose of 100 mg Sildenafil IBSA oral film without water (T1), a single dose of 100 mg Sildenafil IBSA oral film with water (T2) and a single dose of Viagra® film-coated tablet (R; one tablet with water) will be administered under fed conditions to the study subjects in three study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 5 days between the three administrations. The investigational products will be orally administered on day 1 of each study period at 08:00±1 h as follows: ➢ T1: one Sildenafil IBSA 100 mg OF will be administered to the subjects without water. For the administration, the Investigator/deputy will place the film directly on the subject's tongue. Subjects will let the oral film dissolve completely in their mouth (without swallowing or breaking it). ➢ T2: one Sildenafil IBSA 100 mg OF will be administered to the subjects with water. For the administration, the Investigator/deputy will place the film directly on the subject's tongue. Subjects will let the oral film dissolve completely in their mouth (without swallowing or breaking it). After complete film dissolution, the subjects will drink 240 mL of still mineral water. ➢ R: one Viagra® 100 mg film-coated tablet will be administered to the subjects together with 240 mL of still mineral water. The tablet will be completely swallowed and will not be chewed or broken.
Objective: To compare the bioavailability of sildenafil and its metabolite N-desmethyl-sildenafil after single dose of the Test product without water (T1), Test product with water (T2) and Reference product (R), administered to healthy men under fed conditions.
End-points: **Primary end-point:** To evaluate the rate (C_{max}) and extent (AUC_{0-t} and $AUC_{0-\infty}$, if feasible) of sildenafil absorption in plasma after single dose of T1, T2 and R under fed conditions. **Secondary end-points:** ➢ To describe the plasma pharmacokinetic (PK) profile of sildenafil after single dose of T1, T2 and R under fed conditions ➢ To evaluate the PK profile of plasma N-desmethyl-sildenafil after single dose of T1, T2 and R under fed conditions ➢ To collect safety data after single dose of T1, T2 and R under fed conditions
Study variables: **Primary variables:** C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (if feasible) of plasma sildenafil **Secondary variables:** ➢ t_{max}, F_{rel} and, if feasible, $t_{1/2}$, λ_z and of plasma sildenafil ➢ C_{max}, AUC_{0-t}, t_{max}, F_{rel} and, if feasible, $AUC_{0-\infty}$, $t_{1/2}$, and λ_z of plasma N-desmethyl-sildenafil;

STUDY SYNOPSIS (cont.)

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

Analytics: Sildenafil free base and its metabolite N-desmethyl-sildenafil will be determined in plasma at Ardena Bioanalysis B.V., the Netherlands, and at Syneos Health Clinique Inc., Canada, using validated LC-MS/MS methods. The bioanalysis will be performed in compliance with GCP and in accordance with the applicable principles of Good Laboratory Practice (GLP), as defined by OECD, in a GLP compliant facility

Safety and tolerability assessments: TEAEs; vital signs (blood pressure, heart rate); body weight; physical examinations; laboratory tests and ECG.

Sample size: Thirty-six (36) healthy men will be included in the study. The sample size is not based on any statistical evaluation. Drop-out subjects will not be replaced.

Main selection criteria:
Inclusion criteria:
1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males, 18-55 years old inclusive
3. *Body Mass Index*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study

Exclusion criteria:
1. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities; out of range intervals (PR < 110 msec, PR > 200 msec, QRS < 60 msec, QRS >110 msec and QTc > 440 msec)
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study; 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 and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; 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 medications and herbal remedies, for 2 weeks before the start of the study. Organic nitrates will not be allowed for 28 days 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 2015-2020], 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 life style 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 and virology ➢ Urine multi-drug kit test ➢ Adverse event (AE) 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 clinical phase source document only, and will not be transferred to the Sponsor
Period 1 - Visit 2	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomisation ➢ Check of AEs and concomitant medications	Arrival at the clinical centre in the evening. Confinement until the morning of day 2. Standardized low-fat dinner. Fasting for approximately 10 h (overnight).
Period 1 - Visit 3	*Days 1-2*	➢ Investigational product administration at 08:00 ± 1 h (day 1) - 30 min after start of breakfast ➢ Vital signs (blood pressure, heart rate) measurement at pre-dose (0), 1.5 and 24 h post-dose ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0) and 6, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ ECG at 24 h post-dose ➢ Check of AEs and concomitant medications	<u>Day 1</u> Standardized high-fat and high caloric breakfast starting at 30 min pre-dose. Breakfast must be completed within 30 min from start. Standardized lunch and dinner at about 13:00 (5 h post-dose) and 20:00 (12 h post-dose), respectively. <u>Day 2</u> Discharge from the clinical centre in the morning, after the 24 h post-dose blood sample collection, ECG recording 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, continued:			
Wash-out	*At least 5 days*	A wash-out interval of at least 5 days will elapse between the two administrations of Periods 1 and 2	
Period 2 - Visit 4	*Day -1*	As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
Period 2 - Visit 5	*Days 1-2*	As Visit 3	As Visit 3
Wash-out	*At least 5 days*	A wash-out interval of at least 5 days will elapse between the two administrations of Periods 2 and 3	
Period 3 - Visit 6	*Day -1*	As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
Period 3 - Visit 7	*Days 1-2*	As Visit 3	As Visit 3
Final Visit/ETV	*Day 2 of period 3 or ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ ECG recording, in case of ETV only ➢ Vital signs (blood pressure, heart rate), in case of ETV only ➢ Laboratory analyses as at screening, with the exception of virology ➢ Check of AEs and concomitant medications	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions
During each study period, the subjects will be confined from the evening preceding the investigational product administration (study day -1) until the morning of day 2. On day -1 of each period, a standardized low-fat dinner will be served after confinement. Then the subjects will not take any food or drinks (except water) for approximately 10 h (i.e. overnight). On day 1 of each study period, before investigational product administration, all subjects will receive a high-fat and high-caloric breakfast starting 30 min pre-dose and will complete their breakfast within 30 min from start. A standardized lunch and dinner will be served at approximately 5 h and 12 h post-dose (at approximately 13:00 and 20:00). 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 lunch and dinner only; any other coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden. In particular, grapefruit will be forbidden for 24 h before the first investigational product administration until the end of the study. The subjects will be allowed to smoke 3 cigarettes during confinement (1 cigarette after each meal, with the exclusion of breakfast). Routine ambulant daily activities will be strongly recommended, while hazardous, strenuous or athletic activities will not be permitted.		

STUDY SYNOPSIS (cont.)

Data analysis: The data documented in this study and the measured clinical parameters will be presented using classic descriptive statistics for quantitative variables and frequencies for qualitative variables. The pharmacokinetic analysis will be performed using Phoenix WinNonlin® version 6.3 or higher (Pharsight Corporation) and SAS® version 9.3 (TS1M1) for Windows® or higher. The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) for Windows® or higher. Sildenafil and N-desmethyl-sildenafil C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (if feasible) will be compared between T1 vs. R, T1 vs. T2 and T2 vs. R using analysis of variance for a cross-over design on log-transformed data. Period, treatment, sequence and subject within sequence will be taken into account as sources of variation. The 90% confidence intervals of the T1/R, T1/T2 and T2/R ratios of the PK parameters geometric means will be calculated. Sildenafil and N-desmethyl-sildenafil t_{max} will be compared between treatments using the non-parametric Wilcoxon signed-rank test.
Timing: EC meeting: JUL20; planned clinical phase: DEC20-JAN21

4 STUDY SCHEDULE

ACTIVITIES	Screening	PERIOD 1, 2, 3 (wash-out≥5 days)		Final visit/ETV[8]
Visit	**V1**	**V2, V4, V6**	**V3, V5, V7**	
	Day -21/-2	**Day -1**	**Days 1-2**	**Day 2[9]**
Informed consent	x			
Demography	x			
Lifestyle	x			
Medical and surgical history	x			
Physical examination	x			x
Previous and concomitant medications	x	x	x	x
Height	x			
Body Weight	x			x
Laboratory analysis	x			x
Virology	x			
Urine multi-drug kit test	x	x		
Blood pressure and heart rate	x		x[1]	x[8]
Alcohol breath test		x		
ECG	x		x[2]	x[8]
Inclusion/exclusion criteria	x	x[3]		
Subject eligibility	x	x[3]		
Enrolment and randomisation		x[3]		
Confinement		x	x[11]	
Discharge			x[11]	
Investigational product administration[4]			x	
Blood sampling[5]			x	
Standardised meals		x[6]	x[7]	
Adverse event monitoring[10]	x	x	x	x

1. *At pre-dose (0), 1.5 and 24 h post-dose. The Period 3 - 24 h check will correspond to the final assessment*
2. *At 24 h post-dose. The Period 3 - 24 h recording will correspond to the final assessment*
3. *Only at Visit 2*
4. *On day 1 - at 8:00 ± 1 h (30 min after start of high-caloric, high-fat breakfast)*
5. *At pre-dose (0) and 6, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h post-dose*
6. *Standardised low-fat dinner*
7. *High-fat high-caloric breakfast; standardised lunch and dinner (day 1)*
8. *Early termination visit (ETV) in case of premature discontinuation*
9. *Final visit on day 2 of Period 3 after the 24h post-dose blood sampling and safety assessments*
10. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/ETV*
11. *Confinement from day -1 (evening) up to the morning of day 2*

5 TABLE OF CONTENTS

5.1 TABLES

LIST OF ABBREVIATIONS

γ-GT	γ-Glutamyl transpeptidase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOAC	Attributable-Legible-Contemporaneous-Original-Accurate-Complete
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from time zero to time t
$AUC_{0-\infty}$	Area under the concentration vs. time curve up to infinity
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
BW	Body weight
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
cGMP	Cyclic guanosine monophosphate
CI	Confidence Interval
C_{max}	Peak drug concentration
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically Significant
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
DSU	Drug Safety Unit
EC	Ethics Committee
ECG	Electrocardiogram
ED	Erectile Dysfunction
EMA	European Medicines Agency
ETV	Early Termination Visit
FDA	Food Drug Administration
F_{rel}	Relative Bioavailability
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Mean Platelet Volume
N	Normal
NA	Not Applicable
NC	Not calculated
NCS	Not clinically significant
OF	Oral film
OTC	Over The Counter
PDE	Phosphodiesterase

PDE5	Guanosine monophosphate (cGMP)-specific phosphodiesterase type 5
PE	Point Estimate
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R	Reference treatment
RBC	Red Blood Cells
RSI	Reference safety information
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1	Test treatment 1
T2	Test treatment 2
TEAE	Treatment-Emergent Adverse Event
THC	delta-9-tetrahydrocannabinol
$t_{1/2}$	Half-life
t_{max}	Time to achieve C_{max}
USDA	United States Department of Agriculture
WBC	White Blood Cells
WHODDE	World Health Organisation Drug Dictionary Enhanced

6 INTRODUCTION

6.1 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 (ED) is defined as the persistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual performance.

Sildenafil is a selective 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. PDE5 inhibitors are currently the first-line therapy for ED 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 ED (1).

6.2 Pharmacokinetics

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations (C_{max}) are reached within 30 to 120 min (median of 60 min) after oral administration under fasting conditions. The mean absolute oral bioavailability is 41% (range 25-63%). AUC and C_{max} increase proportionally over the recommended oral dose range (25-100 mg). When sildenafil is taken after a heavy and fatty meal, the rate of absorption is reduced with a mean delay in t_{max} of 60 min and a mean reduction in C_{max} of 29% (2, 3).

The mean steady state sildenafil volume of distribution is 105 L, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean C_{max} is approximately 440 ng/mL. Since sildenafil (and its major circulating N-desmethyl metabolite) is bound to plasma proteins in the amount of 96%, this results in mean free plasma C_{max} of sildenafil equal to 18 ng/mL (38 nM). Protein binding is independent of total drug concentrations. In healthy volunteers receiving a 100 mg single dose sildenafil, less than 0.0002% (average 188 ng) of the administered dose is present in ejaculate 90 min after dosing (2, 4).

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 of approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those found for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h (5).

The total sildenafil body clearance is 41 L/h with a resultant terminal phase half-life of 3-5 h. After oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose) (6).

6.2.1 Phase I PK study of sildenafil oral film 100 mg

In a previous single dose, randomised, 2-way cross-over Phase I study, conducted on 54 healthy men aged 36.3±8.6 years, and administered under fasting conditions one single dose of Sildenafil IBSA 100 mg oral film and Viagra® 100 mg film-coated tablet, Pfizer Limited UK, bioequivalence was proven in terms of rate and extent of sildenafil absorption. In addition, the plasma PK profile of the main sildenafil metabolite N-desmethyl-sildenafil was described and safety data were collected after the two treatments (7, 8).

In particular, mean sildenafil plasma concentration-time profiles up to 24 h after single dose administration of Test and Reference were nearly superimposable. The mean plasma sildenafil PK parameters and the results of their statistical comparisons are summarised in the table below.

Table 6.2.1.1 Main sildenafil PK parameters and the results of their comparisons

Sildenafil PK parameters	Test	Reference	Point estimate	90% CI	Friedman test p-value
C_{max} (ng/mL)	645.30±281.83	664.96±317.91	99.53%	90.33 – 109.68%	--
AUC_{0-t} (ng/mL×h)	1971.10±978.16	1900.25±957.31	105.00%	99.38 – 110.94%	--
$AUC_{0-\infty}$ (ng/mL×h)	2001.10±1008.96	1932.13±987.70	104.79%	99.20 – 110.71%	--
t_{max} (h)	0.75 (0.50-3.00)	0.75 (0.25-2.50)	--	--	0.6121

Values are arithmetic means±SD, except for t_{max}: median (range); Point estimate: Test/Reference ratio of geometric means; CI: confidence interval

The bioequivalence test was fully satisfied for sildenafil C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, with the 90% confidence interval (CI) of the Test/Reference ratio of geometric means fully comprised within the 80.00-125.00% acceptance range. In addition, no significant differences in sildenafil t_{max} values between products were observed.

Also the mean plasma concentration-time profiles of the sildenafil metabolite N-desmethyl-sildenafil after single dose administration of Test and Reference were nearly superimposable and the 90% confidence interval for N-desmethyl-sildenafil C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ within the acceptance limits of 80.00 to 125.00%, as summarised in the table below.

Table 6.2.1.2 Main N-desmethyl-sildenafil PK parameters and the results of their comparisons

N-desmethyl-sildenafil PK parameters	Test	Reference	Point estimate	90% confidence intervals	Friedman test p-value
C_{max} (ng/mL)	162.85±68.59	168.63±72.17	98.21%	90.81 – 106.22%	--
AUC_{0-t} (ng/mL×h)	600.90±309.18	568.43±253.58	103.40%	98.18 – 108.90%	--
$AUC_{0-\infty}$ (ng/mL×h)	625.66±322.43	593.65±274.01	103.61%	98.65 – 108.82%	--
t_{max} (h)	0.75 (0.50-3.00)	0.75 (0.25-3.00)	--	--	0.0863

Values are arithmetic means±SD, except for t_{max}: median (range); Point estimate: Test/Reference ratio of geometric means; CI: confidence interval

6.3 Safety

The good tolerability and safety profile of sildenafil for treating ED was established in approximately 74 double-blind placebo-controlled trials performed in more than 9000 patients, confirming that sildenafil is well tolerated at the recommended dose regimen (1).

In the previous Phase I study of Sildenafil IBSA 100 mg oral film vs. Viagra® 100 mg film-coated tablet, Pfizer Limited UK (7), detailed in § 6.2.1 above, the most common Treatment-Emergent Adverse Event (TEAE) was headache which was reported by 13.2% subjects with the Test and by 17.0% subjects with the Reference product followed by flushing (5.7% subjects with Test and 3.8% with Reference), dizziness (5.7% and 1.9% subjects with Test and Reference, respectively), nausea and vomiting (3.8% with Test and 1.9% with Reference for both events) and presyncope (1.9% for both Test and Reference products).

No significant effects of either treatment on vital signs, body weight or electrocardiograms results were observed. One subject experienced a transient AST increase, which was judged by the Investigator as possibly related to the Reference treatment and did not give rise to any safety concern. No other significant effects of either treatment on laboratory parameters were observed.

6.4 Rationale

IBSA Institut Biochimique S.A., Switzerland, developed a sildenafil oral film (OF) containing sildenafil citrate (9), to meet the arising interest for an oral film sildenafil formulation, which dissolves very rapidly (within 1 minute) in the oral cavity without drinking or chewing, and to provide an alternative to the marketed products for ED treatment.

The objective of the present single dose, randomised, 3-way cross-over study is to compare the bioavailability of Sildenafil IBSA 100 mg oral film (Test) and Viagra® 100 mg film-coated tablet, Pfizer Laboratories Div. Pfizer Inc. NY US (Reference) in terms of rate and extent of sildenafil plasma absorption after single dose administration to healthy male volunteers under fed conditions. In addition, sildenafil bioavailability will be compared after administration under fed conditions of the Test product with water vs. Test product without water and vs. Reference product with water. The intake of the Test product with and without water is foreseen by the product labelling. The rationale for an arm with water in the present study is to have a set of data with the same conditions as for the Reference products in terms of stomach content (food and beverage volume).
The study results will be used for the Sildenafil oral film registration procedure in the US.

6.5 Risks and benefits

On the basis of sildenafil 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 study in healthy men (§ 6.3), the reported TEAEs were, in order of decreasing frequency, headache, flushing, dizziness, nausea/vomiting and presyncope.

The most common known adverse events (AEs) of sildenafil are headache, followed by dizziness, visual disorders and colour distortion, flushing, nasal congestion, nausea and dyspepsia (1).

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

No specific benefits for the participants in the current study are foreseen.

7 STUDY OBJECTIVES

The objective of the study is to compare the bioavailability of sildenafil and its metabolite N-desmethyl-sildenafil after single dose of the Test product without water (Test treatment 1; T1), Test product with water (Test treatment 2; T2) and Reference product (Reference treatment; R), administered to healthy men under fed conditions.

7.1 Primary end-point

- To evaluate the rate (C_{max}) and extent (AUC_{0-t} and $AUC_{0-\infty}$, if feasible) of sildenafil absorption in plasma after single dose of T1, T2 and R under fed conditions.

7.2 Secondary end-points

- To describe the plasma pharmacokinetic (PK) profile of sildenafil after single dose of T1, T2 and R under fed conditions
- To evaluate the PK profile of plasma N-desmethyl-sildenafil after single dose of T1, T2 and R under fed conditions
- To collect safety data after single dose of T1, T2 and R under fed conditions.

8 CLINICAL SUPPLIES

8.1 Treatment

8.1.1 Description of products

The analytical certificate of the Test investigational medicinal product (IMP) will be enclosed with the study products and attached to the final report.

8.1.1.1 Test product

TEST (T)

IMP	Sildenafil IBSA 100 mg OF
Active substance	Sildenafil (as sildenafil citrate)
Distributor	IBSA Institut Biochimique S.A., Switzerland
Manufacturer (active substance)	Pharmaceutical Works Polpharma S.A., Poland
Manufacturer (finished product)	Altergon Italia S.r.l., Italy
Pharmaceutical form	Oral film (OF)
Dose	100 mg sildenafil (as sildenafil citrate)
Administration route	Oral

The Test product will be administered without water (Test treatment 1) and with water (Test treatment 2), as detailed in § 8.1.3.

8.1.1.2 Reference product

REFERENCE (R)

IMP	Viagra® 100 mg film-coated tablet
Active substance	Sildenafil (as sildenafil citrate)
Distributor	Manufacturer: Pfizer, Made in Ireland Marketing Authorization Holder: Distributed by Pfizer Labs, Division of Pfizer Inc NY, NY 10017, USA
Pharmaceutical form	Film-coated tablet
Dose	100 mg sildenafil (as sildenafil citrate)
Administration route	Oral

8.1.2 Dose regimen

A single dose of 100 mg Sildenafil IBSA oral film without water (T1), a single dose of 100 mg Sildenafil IBSA oral film with water (T2) and a single dose of Viagra® film-coated tablet (R; one tablet) will be administered to the study subjects in three study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 5 days between the

three administrations. The Test and Reference investigational products will be administered under fed conditions (see § 8.1.3).

8.1.3 Route and method of administration

Test (T) and Reference (R) products will be orally administered on day 1 of each study period at 08:00±1 h as follows:

- Test treatment 1 (T1): one Sildenafil IBSA 100 mg OF will be administered to the subjects without water. For the administration, the Investigator or his 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 oral film 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. When the subject indicates complete disintegration of the oral film, a visual inspection will be performed.
  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 one min of the administration, his mouth will be checked by the Investigator. Film dissolution times will be collected in the specific source documents and subjects' CRFs.

- Test treatment 2 (T2): one Sildenafil IBSA 100 mg OF will be administered to the subjects with water. For the administration, the Investigator or his 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 oral film 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. When the subject indicates complete disintegration of the oral film, a visual inspection will be performed and dissolution time will be assessed and recorded as detailed for T1 above. After complete film dissolution, the subjects will drink 240 mL of still mineral water.

- Reference treatment (R): one Viagra® 100 mg film-coated tablet will be administered to the subjects together with 240 mL of still mineral water. The tablet must be swallowed whole and must not be chewed or broken.

The Investigator or deputy will check that the investigational products have been correctly taken by the subjects.

The subjects will receive the three investigational treatments in the three study periods under fed conditions, i.e. 30 min after starting a high-fat and high-caloric breakfast (see below).

In details, on day 1 after pre-dose blood sample collection and 30 min pre-dose, the subjects will start to eat a high-fat and high-caloric breakfast and will be instructed to complete their meal within 30 min from start.

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 8.1.3.1 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	0	35	4	150
Olive oil white bread	40	2	20	4	100

A deputed clinical staff member will check that breakfast is completed within 30 min from its start. The Investigator will check that all subjects take the investigational products appropriately.

Further details on the administration procedure will be given in the study manual.

8.1.4 Investigational product distribution

Test and Reference investigational products will be administered by the Investigator or his deputy, as detailed in § 8.1.3. The investigational products will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

8.2 Packaging and labelling

The Sponsor will send to the clinical centre an adequate supply of Test and Reference products as well as retention samples in agreement with FDA recommendations (21 CFR 320.38 and 320.63) (11, 12).

Each Sildenafil IBSA OF will be packed in a PET/Foil Extrusion laminate sachet (primary packaging).

Test and Reference 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 and where/if applicable:

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, the name/identifier and strength/potency

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

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

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

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

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

h. The storage conditions

i. 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

j. "Keep out of reach of children"

Labels will be in English.

The investigational products will be additionally labelled for dosing and dispensed by CROSS Research SA. Further details will be given in the study manual.

8.3 Storage conditions

The IMP will be stored in the original packaging, at room temperature (15 – 25°C) in a dry locked place, sheltered from humidity.

8.4 Drug accountability

Test and Reference investigational products will be provided directly to the Investigator by the Sponsor, in excess of the amount necessary for the study conduction, according to the FDA requirements (11, 12).

After receipt of the investigational products' supply, the Investigator or 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 provided by the Sponsor will either be destroyed on site (upon Sponsor written authorisation) or returned to the Sponsor, after assessment of drug accountability.

9 INVESTIGATIONAL PLAN

9.1 Overall study design

This is a single dose, randomised, open-label, 3-way cross-over, fed conditions, bioavailability study. The study will be performed in one clinical site.

9.2 Discussion of design

The study has been designed taking into consideration the following US Department of Health and Human Services Food and Drug Administration (FDA) Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies*, Center for Drug Evaluation and Research CDER December 2002 BP (13); *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations*, CDER March 2014 Biopharmaceutics - *Draft* (14), *Bioavailability Studies Submitted in NDAs or INDs*, CDER February 2019 Clinical Pharmacology - *Draft* (15).

The sample size for this study was not calculated through any statistical calculation due to the lack of previous informative data on the bioavailability of Viagra® 100 mg film-coated tablet administered in fed conditions. .
The dose of 100 mg of sildenafil was chosen on the basis of the clinical practice and the recommended dose regimen of 25-100 mg.

The investigation will be performed under fed conditions and the results of the study will be used for the Sildenafil oral film registration procedure in the US.

Each randomised subject will be allocated to one sequence of treatments according to a computer generated randomisation list (see § 13.1) and to the 3-way cross-over design.

An open-label design is used since the primary end-point of the study is based on objective measurements of sildenafil 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 sildenafil and are the same as for previous Phase I studies (7, 8, 16). Wash-out interval between subsequent administrations is based on sildenafil half-life and is the same used in the other Phase I studies.

10 STUDY POPULATION

10.1 Target population

Healthy men will be enrolled. Drop-outs will not be replaced.

10.2 Inclusion criteria

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

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males, 18-55 years old inclusive
3. *Body Mass Index (BMI)*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure (SBP) 100-139 mmHg, diastolic blood pressure (DBP) 50-89 mmHg, heart rate (HR) 50-90 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study

10.3 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; out of range intervals (PR < 110 msec, PR > 200 msec, QRS < 60 msec, QRS >110 msec and QTc > 440 msec)
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study; 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 and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study; 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. Organic nitrates will not be allowed for 28 days 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 2015-2020 (17)], 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

10.3.1 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.
Paracetamol will be allowed as therapeutic counter-measure for adverse events (AEs) according to the Investigator's opinion.
The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the Investigator, together with the Sponsor, considers it could affect the study assessments or outcome.

11 STUDY SCHEDULE

The schedule of the study is summarised at page 11.

11.1 Study visits and procedures

Each study subject will undergo 8 visits.

The study protocol foresees 3 periods separated by wash-out intervals of at least 5 days. Minimum study duration will be 14 days, screening visit included. The maximum study duration will depend on the actual screening day and wash-out intervals duration. A written informed consent will be obtained before any study assessment or procedure.

The first subject first visit (FSFV) is defined as the first visit performed at the clinical centre by the first screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the clinical centre 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. Additional safety follow-up visits (if needed) may be performed after the LSLV.

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – Visit 1: between day -21 and day -2
  - Period 1 – Visit 2: day -1

- **Interventional phase**
  - Period 1 – Visit 3: days 1-2
  - Wash-out interval of at least 5 days
  - Period 2 – Visit 4: day -1
  - Period 2 – Visit 5: days 1-2
  - Wash-out interval of at least 5 days
  - Period 3 – Visit 6: day -1
  - Period 3 – Visit 7: days 1-2

- **Final phase**
  - Final Visit (Period 3, day 2)/Early Termination Visit (ETV). In case of early discontinuation, discontinued subjects will undergo an ETV

Study activities and procedures are detailed below:

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 life style 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 and virology ➢ Urine multi-drug kit test ➢ Adverse event (AE) 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 clinical phase source document only, and will not be transferred to the Sponsor
Period 1 - Visit 2	*Day -1*	➢ Alcohol breath test ➢ Urine multi-drug kit test ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomisation ➢ Check of AEs and concomitant medications	Arrival at the clinical centre in the evening Confinement until the morning of day 2. Standardized low-fat dinner. Fasting for approximately 10 h (overnight).
Period 1 - Visit 3	*Days 1-2*	➢ Investigational product administration at 08:00 ± 1 h (day 1) - 30 min after start of breakfast ➢ Vital signs (blood pressure, heart rate) measurement at pre-dose (0), 1.5 and 24 h post-dose ➢ Blood sample collection for pharmacokinetic analysis at: pre-dose (0) and 6, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h post-dose ➢ ECG at 24 h post-dose ➢ Check of AEs and concomitant medications	<u>Day 1</u> Standardized high-fat and high caloric breakfast starting at 30 min pre-dose. Breakfast must be completed within 30 min from start. Standardized lunch and dinner at about 13:00 (5 h post-dose) and 20:00 (12 h post-dose), respectively. <u>Day 2</u> Discharge from the clinical centre in the morning, after the 24 h post-dose blood sample collection, ECG recording and vital signs check. Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

Wash-out	*At least 5 days*	A wash-out interval of at least 5 days will elapse between the two administrations of Periods 1 and 2	
Period 2 -	*Day -1*	As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
Period 2 -	*Days 1-2*	As Visit 3	As Visit 3
Wash-out	*At least 5 days*	A wash-out interval of at least 5 days will elapse between the two administrations of Periods 2 and 3	
Period 3 -	*Day -1*	As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	As Visit 2
Period 3 -	*Days 1-2*	As Visit 3	As Visit 3
Final Visit/ETV	*Day 2 of period 3 or ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ ECG recording, in case of ETV only ➢ Vital signs (blood pressure, heart rate), in case of ETV only ➢ Laboratory analyses as at screening, with the exception of virology ➢ Check of AEs and concomitant medications	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

11.2 Diet and lifestyle

On day -1 of each period, a standardized low-fat dinner will be served after confinement. Then the subjects will not take any food or drinks (except water) for approximately 10 h (i.e. overnight).

On day 1 of each study period, before investigational product administration, all subjects will receive a high-fat and high-caloric breakfast starting 30 min pre-dose and will complete their breakfast within 30 min from start. A standardized lunch and dinner will be served at approximately 5 h and 12 h post-dose (at approximately 13:00 and 20:00). Water will be allowed as desired except for 1 h before and 1 h after investigational product administration.

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.

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 lunch and dinner only; any other coffee, tea or food containing xanthines (i.e. coke, chocolate, etc.), alcohol and grapefruit will be forbidden. In particular, grapefruit will be forbidden for 24 h before the first investigational product administration until the end of the study. The subjects will be allowed to smoke 3 cigarettes during confinement (1 cigarette after each meal, with the exclusion of breakfast).

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

11.2.1 Restrictions

During each study period, the subjects will be confined from the evening preceding the investigational product administration (study day -1) until the morning of day 2.

During confinement, hazardous, strenuous or athletic activities will not be permitted.

12 DESCRIPTION OF SPECIFIC PROCEDURES

12.1 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 § 16), 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 case report forms (CRFs).

12.1.1 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]).

12.1.2 Vital signs

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

- Screening
- In each study period at pre-dose (0), 1.5 and 24 h post-dose. The 24 h measurement of Period 3 will correspond to the final assessment
- At ETV, if applicable

12.1.3 ECGs

12-Leads ECGs will be performed in supine position at:

- Screening
- In each study period at 24 h post-dose. The 24 h recording of Period 3 will correspond to the final assessment
- At ETV, if applicable

Date/time of the ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs (see § 16). Hard copies of the ECGs will be attached to the individual CRFs.

12.2 Clinical laboratory assays

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

Haematology
Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, haemoglobin (conv. units), haemoglobin (IS units), haematocrit, MCV, MPV, 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

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, yeast, Trichomonas

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

A urine drug test will be performed at the clinical centre at screening and on day -1 of each period, using a urine multi-drug kit. The following drugs will be assessed: cocaine, amphetamine, methamphetamine, cannabinoids (delta-9-tetrahydrocannabinol - THC), opiates and ecstasy.

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

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs (see § 16). Hard copies of the laboratory print-outs will be attached to the CRFs.

12.3 Sampling for pharmacokinetic analysis

12.3.1 Venous blood sampling

Venous blood samples (9 mL) will be collected from a forearm vein on days 1-2 of each period at the following times:

- pre-dose (0) and 6, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h post-dose

Actual sampling times for each subject will be recorded in the individual CRFs. Deviations in actual sampling times should not exceed the recommended ranges reported in the following table.

Table 12.3.1.1 Tolerance ranges for the scheduled sampling times

Sampling time	Tolerance range
Pre-dose (0)	Within 40 min before IMP administration*
6 min, 15 min	0 min
30 min	± 1 min
45 min	± 2 min
1, 1.25, 1.5 h	± 3 min
2, 2.5, 3, 4, 6, 8 h	± 5 min
12, 16, 24 h	± 10 min

**Before the high-fat, high caloric breakfast (§ 8.1.3).*

Any deviations outside the recommended ranges will be verified through Data Clarification Forms (DCFs) and will not automatically lead to the exclusion of the concerned subjects from the PK Set (see § 15.1).

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 7 mL will be collected from the catheter and transferred with a syringe into heparinised tubes (Li-heparin).

The samples will be stored on ice for a maximum of 20 min and then centrifuged at 4° C for 10 min at 2500 g to obtain plasma. Each plasma sample will be immediately divided into 3 aliquots, P1, P2 and P3, in pre-labelled polypropylene tubes, and stored frozen at ≤-20° C.

If any clinical assessment, such as vital signs measurement or ECG recording, is foreseen at the same time-point as blood sampling for PK analysis, blood collection will be performed at the scheduled time. However, vital signs and ECG parameters can be influenced by the blood sampling. Therefore, these assessments can be performed within 30 min before pre-dose (0 h) and within 10 min before the other scheduled PK time-points. Since vital signs measurement

and ECG recording will be performed for safety reasons only, deviations from the planned time schedule will be considered not relevant.

12.3.2 Analytics

Sildenafil free base and its metabolite N-desmethyl-sildenafil will be determined in plasma at Ardena Bioanalysis B.V., the Netherlands, using a validated LS-MS/MS method.
Further analyses for the determination of sildenafil free base and its metabolite N-desmethyl-sildenafil will be conducted at Syneos Health Clinique Inc., Canada using a validated LS-MS/MS method.

The bioanalysis will be performed in compliance with GCP and in accordance with the applicable principles of Good Laboratory Practice (GLP), as defined by OECD, in a GLP compliant facility.

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

12.3.3 Labelling, storage and transport of samples

12.3.3.1 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-20-346 - Sponsor code 20CH-SDF10
Subject number	001-036
Tube identification	P1/P2/P3
Period	1 or 2 or 3
Scheduled sampling time	as h; see § 12.3.1

12.3.3.2 Samples storage and transport

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

All P1 aliquots, packed in sufficient solid CO_2, will be shipped by an authorised courier from CROSS Research Phase I Unit, Switzerland, to the analytical laboratory (Ardena Bioanalysis B.V., the Netherlands; § 21.3).
P1 aliquots will remain stored at the analytical laboratory for a maximum time of 3 months after a QA audited bioanalytical report is issued. Afterwards, the samples will either be destroyed or returned or stored for a longer period in agreement with the Sponsor. In case the sample destruction is chosen, a certificate of destruction will be provided to the Sponsor.

The counter-samples (P2/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 aliquots, or

- sent to a different laboratory, i.e., Syneos Health Clinique Inc., Canada, for reanalysis should this become necessary for analytical reasons

- 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

The counter-samples (P2/P3 aliquots) will also remain stored at the analytical laboratory for a maximum time of 3 months after a QA audited bioanalytical report is issued. Afterwards, the samples will either be destroyed or returned or stored for a longer period in agreement with the Sponsor. In case the sample destruction is chosen, a certificate of destruction will be provided to the Sponsor.

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 is obtained. The subjects may ask to destroy their own samples at any time.

12.4 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:
Treatment T1: 17 samples x 9 mL = 153 mL
Treatment T2: 17 samples x 9 mL = 153 mL
Treatment R: 17 samples x 9 mL = 153 mL

In total 484 mL of blood (not exceeding a normal blood donation) will be withdrawn from each subject.

13 ASSIGNMENT OF STUDY TREATMENT

13.1 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) (18) 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.

13.2 Treatment allocation

Subjects will be assigned to one sequence of the three treatments 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. Treatment assignment will be performed according to CRO SOP 03.78 and will be detailed in a study manual.

13.3 Blinding

This is an open study. No masking procedure will be applied.

14 EVALUATION PARAMETERS

14.1 Study variables

14.1.1 Primary variables

- C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (if feasible) of plasma sildenafil.

14.1.2 Secondary variables

- t_{max}, F_{rel} and, if feasible, $t_{1/2}$ and λ_z of plasma sildenafil;
- C_{max}, AUC_{0-t}, t_{max}, F_{rel} and, if feasible, $AUC_{0-\infty}$, $t_{1/2}$, and λ_z of plasma N-desmethyl-sildenafil;
- TEAEs, vital signs (BP, HR), body weight, physical examinations, clinical laboratory parameters, ECG.

14.2 Pharmacokinetic assessments

14.2.1 Pharmacokinetic parameters

The following PK parameters will be measured and/or calculated for plasma sildenafil and N-desmethyl-sildenafil using the validated software Pharsight Corporation Phoenix WinNonlin® version 6.3 (18) or higher (the actual version will be stated in the final report):

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

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).

14.3 Safety assessments

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

15 STATISTICAL METHODS

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

Not available data will be evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (18) or higher (the actual versions will be stated in the final report).
The statistical analysis of PK parameters will be performed using Phoenix WinNonlin® version 6.3 (18) or higher and SAS® version 9.3 (TS1M1) or higher.

15.1 Analysis Sets

15.1.1 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 is performed through randomised allocation to a treatment sequence.

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

A subject will be defined as randomised in the study when he is assigned to a randomised treatments sequence.

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 randomised subjects who fulfil the study protocol requirements in terms of T1 and R IMP intake and have evaluable PK data readouts for the planned T1 vs R comparison, with no major deviations that may affect the PK results. This analysis set will be used for the statistical comparison of T1 and R treatments
- PK set 2: all randomised subjects who fulfil the study protocol requirements in terms of T2 and R IMP intake and have evaluable PK data readouts for the planned T2 vs R comparison, with no major deviations that may affect the PK results. This analysis set will be used for the statistical comparison of T2 and R treatments.

- PK set 3: all randomised subjects who fulfil the study protocol requirements in terms of T1 and T2 IMP intake and have evaluable PK data readouts for the planned T1 vs T2 comparison, with no major deviations that may affect the PK results. This analysis set will be used for the statistical comparison of T1 and T2 treatments.

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.

15.1.2 Reasons for exclusion from the PK set before the 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 in the respective study periods
- intake of concomitant medications which could render the plasma concentration-time profile unreliable in the respective study periods
- AEs which could render the plasma concentration-time profile unreliable in the respective study periods
- administration errors which could render the plasma concentration-time profile unreliable in the respective study periods
- other events which could render the plasma concentration-time profile unreliable in the respective study periods

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

15.1.3 Reasons for exclusion from the PK set after the bioanalysis

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

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

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

15.2 Sample size and power considerations

Thirty-six (36) healthy men will be enrolled in the study. No formal calculation was performed due to the lack of previous informative data on the bioavailability of Viagra® 100 mg film-coated tablet administered in fed conditions. Discontinued subjects will not be replaced.

15.3 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.

15.4 Drug administration and analysis of film dissolution time

For T1 and T2 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 T1 and T2 treatments.

15.5 Analysis of pharmacokinetic parameters

15.5.1 Descriptive pharmacokinetics

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).

15.5.2 Statistical comparison of pharmacokinetic parameters

According to the FDA Guidance for Industry (13-15), plasma sildenafil and N-desmethyl-sildenafil AUC_{0-t}, $AUC_{0-\infty}$ (if feasible) and C_{max} will be compared between T1 vs. R, T1 vs. T2 and T2 vs. R using analysis of variance (ANOVA) for a cross-over design. 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 sources of variation.
The 90% confidence intervals of the T1/R, T1/T2 and T2/R ratios of the PK parameters geometric means will be calculated.
Sildenafil and N-desmethyl-sildenafil t_{max} will be compared between treatments using the non-parametric Wilcoxon signed-rank test.

15.6 Safety and tolerability evaluation

15.6.1 Adverse events (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 IMP
- TEAEs: all AEs occurring or worsening after the first dose of 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.

15.6.2 Physical examination

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

15.6.3 Laboratory data

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

15.6.4 Vital signs

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

15.6.5 Body weight

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

15.6.6 ECG

Date/time of ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. The overall investigator's interpretation will be summarised using tables of frequency.

16 DEFINITION AND HANDLING OF AEs AND SAEs

16.1 Applicable SOPs

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

16.2 Definitions

➢ **Adverse events (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 Reactions (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 adverse event/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 i.e. as illustrated into the Reference Safety Information (RSI), section "Adverse Reactions" of the SmPC for the Test and the Reference product.

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

- **Pre-treatment AEs (PTAE)**

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.
The following medical occurrences and clinical investigations are the only clinically significant (CS) events which, according to the Investigator's judgment, can be defined and recorded as PTAEs:

- trauma (fractures, sprains, strains, falls, domestic accidents, car accidents, etc.)
- new measurements (vital signs, ECG, laboratory parameters, etc.), which show a clinically significant deviation in comparison with a previous (baseline) measurement performed after the signature of the informed consent
- any disease diagnosed after the anamnesis recorded at visit 1
- physical and mental status changes (pre-syncope, anxiety, dizziness, fainting, etc.).

- **Treatment-emergent AE (TEAE)**
  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").

16.3 Severity classification

Regardless of the classification of an adverse event as serious or non-serious, the severity of an adverse event 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.

16.4 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**

AEs/SAEs which might happen after the patient's inclusion into the study but before the effective study treatment period will be considered as pre-study treatment adverse event (PTAE). The causality assessment for such AEs/SAEs will not be expressed by the Investigator but with the option box "*pre-study treatment adverse event*", being pretty much obvious the relationship cannot stand, lacking the exposure to the IMP. DSU will treat PTAEs as not reasonably related events.

After given the causality assessment the Investigator will evaluate the expectedness.
In order to assess whether an adverse reaction is expected, the dedicated section (Reference Safety Information, RSI) within SmPC for the Test and Reference product will be used.

16.5 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)
Tel +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 and/or the follow-up planned period.

When the Investigator has received knowledge of a SAE, he/she 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/randomization 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 stabilisation in the event of chronicity. In case of hospitalisation 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 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 their 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.

16.6 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.

16.7 Pregnancy

The target population which the protocol is referred to is of male patients.
The metabolism of sildenafil 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 not applicable and no pregnancy reports will be collected or managed, being out of the purposes and design of the protocol.

16.8 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

17 DATA MANAGEMENT PROCEDURES

17.1 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.

17.2 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. 20CH-SDF10), the 3-digit site number (i.e. 001), the 4-digit screening number (e.g. S001, S002, etc.) and the 3-digit 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 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 clinical study report (CSR).

17.3 Database management

The CRO will provide a double data entry with total re-entry of data by a second data entrist and discrepancy resolution by a third individual and will update and verify the database and create the final SAS data sets. The final data file will be transferred to the Sponsor in the agreed format with all the other study documentation.

17.3.1 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 study report.

18 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

18.1 Monitoring

The monitoring visits will be conducted by the appointed study CRA (§ 21.6).

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements and will be detailed in a monitoring plan based on IBSA risk assessment 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.

18.2 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 requirements.

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

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

18.3 Applicable SOPs

The Sponsor, the clinical centre and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for review, if required. AEs, SAEs, SAEs reconciliation and TMF and ISF management will follow IBSA SOPs and Work Instructions (WI).

18.4 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, Independent Ethics Committee (IEC) review, and regulatory inspections.

18.5 Audits and inspections

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

The study may also be inspected by regulatory authorities.

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

19 ETHICAL CONSIDERATIONS

19.1 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.

19.2 Informed consent

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

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

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

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 § 20.3).

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.

19.3 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.

19.4 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.

19.4.1 Primary reason for discontinuation

- **Adverse event**: Any (significant) adverse event that in the opinion of the Investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 16.2.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by Sponsor**: an indication that a clinical study was stopped by its Sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

19.4.2 Discontinuation procedures

For any subject discontinuing the study, the Investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory assays. This examination will verify that all values tested at screening have remained

within a clinically acceptable range (i.e. not clinically significant changes compared to screening)

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

Discontinued subjects will not be replaced.

19.5 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.

20 ADMINISTRATIVE PROCEDURES

20.1 Material supplied to the clinical centre

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

- final version of the study protocol
- CRF for each subject plus some spare copies
- copy of SmPC relative to the Test investigational product and SmPC relative to the Reference investigational product
- informed consent forms

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

20.2 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.

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

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

The Investigator and the Sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirements.

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

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

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

20.4 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.

20.5 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 his/her 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 (see § 17.2). 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.

The processing of personal data by the Sponsor, the CRO and the clinical site shall always be in line with the local regulations, the EU General Data Protection Regulation (GDPR; Regulation EU 679/2016), and the applicable Swiss data protection regulations (Swiss Law 235.1, Federal Act on Data Protection of June 19th, 1992). Suitable written information will be provided to the study subjects at the time of consenting.

20.6 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 clinical study report.

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 clinical study report 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.

21 STUDY RESPONSIBLE PERSONS

21.1 Sponsor

IBSA Institut Biochimique S.A., Via del Piano 29, PO Box 266, CH-6915 Pambio-Noranco, Switzerland
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Fax: +41.58.360.16.55
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Sponsor representatives
Giuseppe Mautone, Head of R&D Scientific Affairs
Valeria Frangione, PhD, R&D Scientific Affairs Manager
Carol Caverzasio, MSc, R&D Scientific Affairs Specialist
Chiara Godina, Qualified Person for Pharmacovigilance

Medical Expert
Gabriele Brunetti, MD

21.2 Institutes performing the study

21.2.1 Clinical centre

CROSS Research S.A. - Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41.91.64.04.450
Fax: +41.91.63.00.511
Email: clinic@croalliance.com

Principal Investigator
Milko Radicioni, MD

21.3 Drug assay

For all aliquots 1 (P1) and part of the aliquots 2 (P2) analysis:
Ardena Bioanalysis B.V.,
W.A. Scholtenstraat 7, PO Box 232, NL-9403 AJ Assen, the Netherlands
Phone: +31.592.344211
Email: elena.mallat@ardena.com

Analytics representative
Elena Mallat, Project Manager

For all aliquots 2 (P2) and all aliquots 3 (P3) analysis:
Syneos Health Clinique Inc.
2500, Einstein Street
Québec (Québec), G1P 0A2
CANADA
Phone: +1.418.5274000

Email: marieeve.coulombe@syneoshealth.com

Analytics representative
Marie-Eve Coulombe, Manager, Bioanalysis

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

21.4 Centralised clinical laboratory

Unilabs Ticino, via Rovere 8, CH-6932 Breganzona, Switzerland
Phone: +41.91.960.73.73
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21.5 Co-ordination, data analysis & reporting

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21.6 Monitoring

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Monitor
Maria Pia Savorelli

22 REFERENCES

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