CLINICAL STUDY PROTOCOL

Study CRO-PK-22-360 - Sponsor code Z7100J02

Bioequivalence study of a new ibuprofen arginine 600 mg tablet formulation versus ibuprofen arginine 600 mg sachet in healthy volunteers

Single centre, single dose, open-label, randomised, two-way, two-stage, cross-over bioequivalence study

Investigational product:	Ibuprofen arginine 600 mg film-coated tablet, Zambon S.p.A., Italy
Reference product:	Espidifen® 600 mg granules for oral solution, Zambon S.A.U., Spain
Sponsor:	Zambon S.p.A., via Lillo del Duca 10, I-20091 Bresso (MI), Italy Phone: +39.02.66.52.41 Fax: +39.02.66.50.14.92 Email: veronica.difonzo@zambongroup.com
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Development phase:	I
Version and date:	CSP final version 1.0, 08JUL2022

This study will be conducted in compliance with the protocol, the principles of Good Clinical Practice [ICH topic E6 (R2)], and with the applicable local regulatory requirements

This document comprises 64 pages

2 PROTOCOL APPROVAL

2.1 SPONSOR

Zambon S.p.A., Italy

Sponsor Representative and Medical Expert
Veronica Di Fonzo, Global Medical Advisor

08/07/2022 _____ Veronica Di Fonzo _____
Date Signature

2.2 INVESTIGATOR

Principal Investigator

I have read this protocol and agree to conduct this study in compliance with the protocol, 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, Arzo, Switzerland

08 JUL 2022 _____
Date

_____
Signature

2.3 CRO

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Biometry Unit Representative
Alessandra Gentili, Biometry Manager, Unit Head

08 JUL 2022 — Date
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3 STUDY SYNOPSIS

Title: Bioequivalence study of a new ibuprofen arginine 600 mg tablet formulation versus ibuprofen arginine 600 mg sachet in healthy volunteers
Protocol number: CRO-PK-22-360/Sponsor code Z7100J02
Clinical phase: Phase I
Study design: Single centre, single dose, open-label, randomised, two-way, two-stage, cross-over bioequivalence study
Planned nr. of centres/countries: 1/Switzerland
Investigator and centre: *Principal Investigator:* Milko Radicioni, MD; CROSS Research Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Investigational product(s): TEST: Ibuprofen arginine 600 mg film-coated tablet, Zambon S.p.A., Italy REFERENCE: Espidifen® 600 mg granules for oral solution, Zambon S.A.U., Spain
Dose regimen: A single oral dose of the test and reference investigational products will be administered to healthy men and women under fasting conditions in two study periods according to a randomised 2-way cross-over design, with a wash-out interval of at least 3 days between the two administrations.
Objectives: **Primary objective:** The primary objective of the study is to evaluate the bioequivalence of the new ibuprofen arginine (IBA) 600 mg film-coated tablet (test, T) versus the marketed IBA 600 mg sachet (reference, R), by assessing rate and extent of absorption of ibuprofen S-enantiomer after single dose administration of the two products in healthy men and women. **Secondary objectives:** Secondary objectives are the following: • to evaluate the pharmacokinetic parameters and the pharmacokinetic profile of ibuprofen S-enantiomer, after single dose administration of test and reference products • to evaluate the pharmacokinetic parameters and the pharmacokinetic profile and to compare the rate (C_{max}) and extent (AUC_{0-t}) of absorption of ibuprofen R-enantiomer, after single dose administration of test and reference products • to evaluate the pharmacokinetic parameters and the pharmacokinetic profile and to compare the rate (C_{max}) and extent (AUC_{0-t}) of absorption of total ibuprofen, calculated as the sum of the two enantiomers, after single oral dose administration of test and reference products • to collect safety and tolerability data of test and reference products after single dose administration.
Variables/endpoints: **Primary variables/endpoints:** • C_{max} and AUC_{0-t} of plasma ibuprofen S-enantiomer after single oral dose of T and R products **Secondary variables/endpoints:** • t_{max}, F_{rel} and, if feasible, $AUC_{0-\infty}$, $t_{1/2}$ and λ_Z of plasma ibuprofen S-enantiomer after single oral dose of T and R products • C_{max}, AUC_{0-t}, t_{max}, F_{rel} and, if feasible, $AUC_{0-\infty}$, $t_{1/2}$ and λ_Z of plasma ibuprofen R-enantiomer after single oral dose of T and R products • C_{max}, AUC_{0-t}, t_{max}, F_{rel} and, if feasible, $AUC_{0-\infty}$, $t_{1/2}$ and λ_Z of total ibuprofen, calculated as the sum of ibuprofen S-enantiomer and R-enantiomer concentrations, after single oral dose of T and R products • TEAEs, vital signs (blood pressure, heart rate), physical examinations, body weight, clinical laboratory parameters.
Analytics: The concentrations of ibuprofen S-enantiomer and R-enantiomer will be determined in plasma samples at Anapharm Europe, S.L.U., Spain, using a fully validated chiral LC-MS/MS method. Analyses will be performed in compliance with GCP regulations, following applicable GLP principles.

STUDY SYNOPSIS (cont.)

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

Sample size: The study will be conducted according to a two-stage design.
24 men and women will be enrolled in study stage 1. No drop out replacement is foreseen. After the end of stage 1, pharmacokinetic parameters will be calculated and an ad interim bioequivalence test will be performed on ibuprofen S-enantiomer C_{max} and AUC_{0-t}. To safeguard the overall type I error, the one-sided α-level of the bioequivalence test will be set to 0.0294 according to the Pocock spending function.
Should bioequivalence be proven with the results of the first stage, the primary objective of the study will be satisfied and the second study stage will not take place.
Should bioequivalence not be proven with the results of stage 1 and with an a posteriori calculated power ≥ 80% for AUC_{0-t} or C_{max}, the study will be stopped without proving bioequivalence.
Should bioequivalence not be proven with the results of the first stage and with an a posteriori calculated power < 80% for both AUC_{0-t} and $C_{max,}$ the overall sample size for the study (stage 1 + stage 2) will be calculated on the basis of the point estimate of the test/reference ratio of the geometric means of 0.95 and of the variance of stage 1. The additional subjects will be enrolled in study stage 2. After completion of stage 2, the pharmacokinetic analysis and the bioequivalence test will be performed on the pooled subjects of both study stages.

Main selection criteria:
Inclusion criteria:

1. *Informed consent*: subjects able to complete and sign the informed consent before inclusion in the study
2. *Sex and Age*: men and women, 18-55 years old inclusive
3. *Body Mass Index*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 60-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study
6. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception:
    a. Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit
    b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
    c. A male sexual partner who agrees to use a male condom with spermicide
    d. A sterile sexual partner

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

Exclusion criteria:

1. *Subjects*: subjects younger than 18 years or older than 55 years, subjects unable to give the informed consent, subjects with cognitive impairment and otherwise non-healthy subjects
2. *SARS-CoV-2 test*: positive Covid-19 Antigen Rapid Test at screening or Day -1
3. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
4. *Physical findings:* clinically significant abnormal physical findings which could interfere with the objectives of the study
5. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
6. *Allergy*: ascertained or presumptive hypersensitivity to the active principle or formulations' ingredients or both; history of anaphylaxis to drugs or allergic reactions in general (in particular to non-steroidal anti-inflammatory drugs), which the Investigator considers may affect the outcome of the study
7. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, immunological or neurological diseases that may interfere with the aim of the study

STUDY SYNOPSIS (cont.)

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

8. *Medications*: medications, including over the counter medications, herbal remedies and vitamins, for 2 weeks before the start of the study. Hormonal contraceptives for women will be allowed
9. *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
10. *Blood donation*: blood donations for 3 months before this study
11. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
12. *Drug test*: positive result at the drug test at screening or Day -1
13. *Alcohol test*: positive alcohol test on Day -1
14. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
15. *Pregnancy (women only)*: positive or missing pregnancy test at screening or Day -1, pregnant or lactating women.

Schedule:

		Day	Procedures/Assessments	Notes
Screening	**Visit 1**	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Covid-19 Antigen Rapid Test ➢ Drug screening test ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, physical abnormalities) ➢ Vital signs (blood pressure, heart rate) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis, virology ➢ Serum pregnancy test (women only) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ AEs monitoring	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source documents only and will not be transferred to the Sponsor
Period 1	**Visit 2**	*Day -1*	➢ Covid-19 Antigen Rapid Test ➢ Alcohol test ➢ Vital signs (blood pressure, heart rate) ➢ Urine pregnancy test (women only) ➢ Drug screening test ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomisation (e.g., 001, 002, etc.) ➢ AEs and concomitant medications	Arrival at the Phase I Unit in the evening Confinement until the evening of Day 1 Standardised dinner Fasting overnight for at least 10 h

STUDY SYNOPSIS (cont.)

Schedule (cont.):				
		Day	**Procedures/Assessments**	**Notes**
Period 1	**Visit 3**	*Day 1*	➢ Investigational product administration at 08:00±1h ➢ Blood sample collection for PK analysis at: pre-dose (0), 5, 10, 20, 30, 40, 50 min and 1, 1.5, 2, 3, 4, 6, 9, 12 h post-dose ➢ Vital signs (blood pressure, heart rate) at 12 h post-dose ➢ AEs and concomitant medications	All subjects will be fasting for 5 h post-dose Standardised lunch at approximately 5 h post-dose Discharge from the Phase I Unit in the evening, after the 12 h post-dose blood sample collection and vital signs check. Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions
Wash-out		*At least 3 days*	➢ A wash-out interval of at least 3 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	
	Visit 5	*Day 1*	➢ As Visit 3	
Final visit/ETV		*Day 1 of period 2 or ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ Vital signs (blood pressure, heart rate) (ETV only) ➢ Laboratory analyses as at screening, with the exception of virology and pregnancy test ➢ AEs and concomitant medications In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reaction
Diet and lifestyle and study restrictions: *During each study period, the subjects will be confined at the Phase I Unit from the evening of Day -1 until the evening of Day 1. During confinement, the subjects will not take any food or drinks, except water, apart from the standardised meals. On Day -1 of each study period, a standardised low-fat dinner will be served, then all the subjects will remain fasted for at least 10 h (i.e., overnight). On Day 1 of each study period, the subjects will remain fasted until 5 h post-dose. Standardised lunch will be served at approximately 5 h post-dose.* *Water will be allowed as desired, except for 1 h before and 1 h after investigational product administration (with the exception of the water taken for products' administration). To maintain an adequate hydration, the subjects will be encouraged to drink at least 150 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.*				

STUDY SYNOPSIS (cont.)

Diet and lifestyle and study restrictions (cont.):
One cup of coffee or tea will be allowed after each meal only; any other coffee, tea or food containing xanthines (i.e., coke, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit will be forbidden from 24 h before the first investigational product administration until the end of the study. One cigarette will be allowed after each meal only.
During confinement, routine ambulant daily activities will be strongly recommended. For the 4 h following the administration, when not involved in study activities, the subjects will remain seated. They will not be allowed to lie down. Hazardous, strenuous or athletic activities will not be permitted.

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

Pharmacokinetic analysis:
A descriptive PK will be presented for ibuprofen S-enantiomer, ibuprofen R-enantiomer and total ibuprofen. The total ibuprofen concentration will be calculated by the CRO Biometry Unit as the sum of ibuprofen S-enantiomer and R-enantiomer concentrations. The results will be displayed and summarised in tables and figures. PK parameters AUC_{0-t} and C_{max} for ibuprofen S-enantiomer, ibuprofen R-enantiomer and total ibuprofen will be analysed using analysis of variance. Before analysis, the data will be transformed using a neperian logarithmic transformation. Analysis of variance will be performed on the data from study stage 1 and, if necessary, on the combined data from stage 1 and stage 2. Treatment, period, sequence, subject (sequence) will be taken into account as sources of variation during the analysis on the data from stage 1. During the analysis on the combined data from stage 1 and stage 2 (if any), stage, treatment, period (stage), sequence, sequence*stage, subject (sequence*stage) will be taken in account as sources of variation.
For both the analysis (stage 1 data) and the final combined analysis (stage 1 and 2 data, if any), acceptance criterion for bioequivalence is that the two-sided 94.12% confidence interval of the T/R ratio of the least-square geometric means of the parameters is within the 80.00-125.00% range, according to the Pocock α spending function.
T_{max} will be analysed using the non-parametric Wilcoxon signed-rank test.

Demography and safety analysis:
Demographic and safety data will be listed and summarised by descriptive statistics or frequency.

Timing: EC meeting: AUG22

4 STUDY SCHEDULE

ACTIVITIES	Screening	PERIOD 1, 2 (wash-out ≥ 3 days)		Final visit/ETV[11]
Visit	**V1**	**V2, V4**	**V3, V5**	
	Days -21/-2	**Day -1**	**Day 1**	**Day 1[12]**
Informed consent	x			
SARS-CoV-2 rapid test	x[1]	x		
Demography	x			
Lifestyle	x			
Medical and surgical history	x			
Physical examination	x			x
Previous/concomitant medications	x	x	x	x
Body weight	x			x
Height	x			
Laboratory analysis	x			x
Virology	x			
Drug screening test	x	x		
Blood pressure and heart rate	x	x	x[10]	x[14]
Pregnancy test	x[2]	x[3]		
ECG	x			
Alcohol test		x		
Inclusion/exclusion criteria	x	x[4]		
Subject eligibility	x	x[4]		
Enrolment and randomisation		x[4]		
Confinement[5]		x	x	
Discharge			x	x
Investigational medicinal product administration			x[7]	
Blood samplings			x[8]	
Standardised meals		x[6]	x[9]	
Adverse events monitoring[13]	x	x	x	x

1. *Covid-19 Antigen Rapid Test immediately after the signature of the informed consent*
2. *Women only - serum β-HCG test*
3. *Women only - urine test*
4. *Only at visit 2*
5. *Confinement from the evening of Day -1 up to the evening of Day 1*
6. *Standardised low-fat dinner*
7. *At 8:00±1 h*
8. *At pre-dose (0), 5, 10, 20, 30, 40, 50 min and 1, 1.5, 2, 3, 4, 6, 9, 12 h post-dose*
9. *Standardised lunch at approximately 5 h post-dose*
10. *At 12 h post-dose*
11. *ETV in case of premature discontinuation*
12. *Final visit on Day 1 of Period 2 after the 12 h post-dose blood sampling and vital signs check*
13. *Adverse events monitored starting at the screening visit, immediately after informed consent, up to the final visit/Early termination visit (ETV)*
14. *At ETV only*

5 TABLE OF CONTENTS

5.1 TABLES

6 LIST OF ABBREVIATIONS

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

MedDRA	Medical Dictionary for Regulatory Activities
N	Normal
NA	Not Applicable
NC	Not Calculated
NCS	Not Clinically Significant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R	Reference product
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product
$t_{1/2}$	Half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to achieve C_{max}
TMF	Trial Master File
USDA	United States Department of Agriculture
WHODDE	World Health Organisation Drug Dictionary Enhanced

7 STUDY RESPONSIBLE PERSONS

7.1 Sponsor

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7.2 Institutes performing the study

7.2.1 Principal Investigator and clinical centre

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

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8 INTRODUCTION

8.1 Background

Ibuprofen, a phenyl propionic acid derivative, is a well-known non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of mild to moderate pain and inflammation. It is generally administered by oral route and topical application, in conditions such as dysmenorrhoea, headache, postoperative pain, dental pain, musculoskeletal and joint disorders (1).

The mechanism of action of ibuprofen has been well studied in humans: ibuprofen has an inhibitory effect on prostaglandin synthesis, specifically on cyclooxygenase activity, exhibiting analgesic, antipyretic and anti-inflammatory properties (2).

Although ibuprofen exists as (-) R and (+) S enantiomers, the anti-inflammatory activity is thought to reside almost exclusively in the S-enantiomer, that has been found to be more potent than the R-isomer in inhibiting prostaglandin synthesis in vitro (2).

Ibuprofen is usually marketed as free acid, but different salts, esters and other derivatives are also used, among which ibuprofen L-arginine.

Ibuprofen L-arginine is a preparation obtained combining the racemic ibuprofen with the amino acid L-arginine. The addition of L-arginine increases the solubility of the active ingredient without affecting its chemical stability. L-arginine offers the advantage of delivering oral racemic ibuprofen in a more efficient way than the standard ibuprofen formulations. This advantage has stimulated in the last years the interest in the clinical evaluation of ibuprofen L-arginine for a quick and effective treatment of acute and chronic pain (2).

8.2 Pharmacokinetics

When orally administered, ibuprofen reaches the maximum plasma levels approximately 1-2 hours after dosing. By comparison, peak plasma levels are reached about 15-20 minutes after administration of ibuprofen L-arginine (shorter t_{max}) (2). Furthermore, administration of oral formulations of ibuprofen L-arginine resulted in C_{max} higher than those obtained after the same dose of standard ibuprofen (2). On the other hand, AUC is not significantly different between the two ibuprofen formulations (2).

Ibuprofen undergoes an extensive hepatic metabolism, with less than 1% of the dose excreted unchanged by the kidney. More than 90% is excreted as pharmacologically inactive metabolites by the kidney, the remaining is possibly excreted in the bile and eliminated via faeces. Excretion is essentially complete within 24 hours (2).
Pharmacokinetic (PK) studies carried out on healthy volunteers demonstrated that the presence of L-arginine provides an enhanced solubility of ibuprofen, increasing its absorption without affecting its bioavailability (2). The outcome is an earlier onset of analgesia, particularly favourable characteristic in those conditions in which a very rapid analgesic effect is required (5, 6).

8.3 Ibuprofen arginine

The Sponsor, Zambon S.p.A., has been working for many years on the development of different oral formulations containing ibuprofen L-arginine (IBA) at different strengths. The first product was registered in Spain in January 1990. Presently, several Zambon formulations containing IBA are authorised in 30 countries (2).

Many clinical studies were carried out on IBA oral formulations in healthy volunteers, in order to investigate the PK profile and safety in comparison to the commercially available ibuprofen.

A single-dose, open-label, randomised, two-treatments, two-period cross-over clinical study was carried out in 18 healthy male volunteers to compare the bioequivalence of two different IBA oral formulations, i.e., IBA 200 mg sachet and IBA 200 mg tablet (7). The mean ibuprofen concentration profiles of the two formulations did not show any statistical difference. Mean rates of elimination were comparable. The 90% CI for AUC, $AUC_{0-\infty}$ and C_{max} were within the accepted bioequivalence ranges of 80-125%.

An open-label, three-period, three treatments cross-over clinical study was conducted in 27 healthy male volunteers to compare the bioequivalence of two different IBA oral formulations (200 mg sachet and 200 mg tablet) versus a commercially available ibuprofen (Motrin® 200 mg tablet) (8). Results are summarised in the table below.

Table 8.3.1 Mean main PK parameters of plasma ibuprofen after oral administration of IBA 200 mg sachet, IBA 200 mg tablet and Motrin® 200 mg tablet

Ibuprofen PK parameters	IBA 200 mg sachet	IBA 200 mg tablet	Motrin® 200 mg tablet
t_{max} (min)	20.83	29.37	78.75
$t_{1/2}$ (h)	1.81	1.78	1.77
C_{max} (µg/ml)	22.83	23.75	19.20
AUC (µg-h/ml)	55.39	58.66	60.35

Both IBA sachet and tablet showed a higher C_{max} and a shorter t_{max} as compared to Motrin® tablet. Moreover, absorption was faster for the IBA sachet than for the IBA tablet. The direct comparison of IBA 200 mg sachet versus IBA 200 mg tablet showed that C_{max} of IBA 200 mg sachet and tablet fall within the 80-125% bioequivalence limits. T_{max}, as expected, was shorter for sachet. Based on the two-sided test rule, all three formulations were equivalent for extent of absorption and elimination. All confidence limits for the AUC ratios fell within the 80-125% bioequivalence limits (2).

IBA 400 mg was investigated in two single-dose, open-label, randomised, two-treatments, two-period, cross-over clinical studies.

A first study compared IBA 400 mg sachet versus ibuprofen 400 mg tablet when administered to 8 healthy male and female volunteers under fasting conditions (9). The results confirmed a significant difference in t_{max}, indicating that the ibuprofen formulation containing L-arginine produces a quicker absorption of the active ingredient, compared to the commercially available tablet formulation, without affecting the bioavailability of ibuprofen (2). Another clinical trial investigated the relative bioavailability of IBA 400 mg tablet versus ibuprofen 400 mg tablet

(Brufen®) in 24 healthy male volunteers (10). The study results indicated a more rapid absorption of ibuprofen from IBA 400 mg tablet than from Brufen® 400 mg tablet, leading to a about 30% higher C_{max} of IBA without any clinically relevant change in AUC or half-life (2). However, the limited number of subjects enrolled in the two studies did not allow any definitive conclusion.

A single-dose, open-label, randomised, cross-over, single and repeated dose clinical study was carried out in 12 healthy male and female volunteers, with the aim of evaluate ibuprofen PK, relative bioavailability and bioequivalence after single and repeated administration of IBA 600 mg sachet and ibuprofen 600 mg tablet (Brufen®) (11). C_{max} values obtained after the 1st dose of the two products were very similar. In addition, a similar extent of exposure was observed by the direct comparison of IBA 600 mg sachet versus ibuprofen 600 mg tablet. However, highly significant differences were found when the mean times to achieve maximum concentrations (t_{max}) were compared (11).

8.4 Rationale

The Sponsor has recently developed a new formulation of IBA 600 mg film-coated tablets, to provide an alternative to the already approved IBA 600 mg sachet for oral solution.

IBA 600 mg film-coated tablet is a similar formulation of an authorised tablet containing IBA 400 mg and presents the same dose as the authorised product Espidifen® 600 mg granules for oral solution. Nevertheless, a request for a biowaiver to the Spanish drug agency was not accepted because the manufacturing process of both strengths is not fully identical and the upwards biowaiver for low solubility drug is not possible. Spanish Health Authorities concluded that a bioequivalence study was necessary.

As highlighted above, previous PK studies investigating IBA 200, 400 and 600 mg racemic compound in different settings showed that it is not possible to predict an outcome.

Furthermore, ibuprofen is a racemate and S-enantiomer is the active form of ibuprofen, predominant after oral administration of racemic compound.

Taken into account the above premises, the present cross-over, two-stage bioequivalence study aims to evaluate the bioequivalence of the new IBA 600 mg film-coated tablet formulation - test product - versus IBA 600 mg sachet - reference product - in terms of rate (C_{max}) and extent (AUC_{0-t}) of absorption of the ibuprofen active S-enantiomer after single dose administration in healthy men and women.

8.5 Risks and benefits

Ibuprofen is a safe product for the treatment of pain, with a well-known safety profile which has remained consistent in the last years. It is well tolerated and is one of the safest NSAID also during long-term treatment.

Adverse events (AEs) are mainly of gastrointestinal type. In detail, very common (≥1/10) AEs includes dyspepsia and diarrhoea. Common (≥1/100 to <1/10) AEs are abdominal pain, nausea, flatulence, headache, dizziness, skin disorder and rash (2).

AEs reported with IBA were similar to those observed in the group of subjects who received ibuprofen comparators. The most frequent AEs experienced with IBA were of gastrointestinal nature, being mainly nausea and vomiting. For details refer to the Investigator's Brochure (IB) (2).

Blood sampling for laboratory and PK analyses 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.

9 STUDY OBJECTIVES

9.1 Study objectives

9.1.1 Primary objective

The primary objective of the study is to evaluate the bioequivalence of the new IBA 600 mg film-coated tablet (test, T) versus the marketed IBA 600 mg sachet (reference, R), by assessing rate and extent of absorption of ibuprofen S-enantiomer after single dose administration of the two products in healthy men and women.

9.1.2 Secondary objectives

Secondary objectives are the following:

- to evaluate the PK parameters and the PK profile of ibuprofen S-enantiomer, after single dose administration of test and reference products
- to evaluate the PK parameters and the PK profile and to compare the rate (C_{max}) and extent (AUC) of absorption of ibuprofen R-enantiomer, after single dose administration of test and reference products
- to evaluate the PK parameters and the PK profile and to compare the rate (C_{max}) and extent (AUC) of absorption of total ibuprofen, calculated as the sum of the two enantiomers, after single oral dose administration of test and reference products
- to collect safety and tolerability data of test and reference products after single dose administration.

10 CLINICAL SUPPLIES

10.1 Treatment

10.1.1 Description of products

The analytical certificates will be supplied with the investigational medicinal products (IMPs).

10.1.1.1 Test product

TEST (T)	
IMP	Ibuprofen as L-Arginine salt
Manufacturer (active substance)	SI GROUP, INC, South Carolina, USA
Manufacturer (finished product)	Zambon S.p.A., Italy
Manufacturer (packaging)	STM Pharma Pro S.r.l., Italy
Pharmaceutical form	Film-coated tablet
Dose	600 mg
Administration route	Oral

10.1.1.2 Reference product

REFERENCE (R)	
IMP	Ibuprofen as L-Arginine salt
Manufacturer (active substance)	HUBEI BIOCAUSE HEILEN PHARMACEUTICAL CO., LTD., Hubei Province, China
Manufacturer (finished product)	Zambon Switzerland Ltd., Switzerland
Manufacturer (packaging)	STM Pharma Pro S.r.l., Italy
Pharmaceutical form	Granules for oral solution
Dose	600 mg
Administration route	Oral

10.1.2 Dose regimen

Each subject will receive a single oral dose of 600 mg of IBA, as film-coated tablet (test product) and granules for oral solution (reference product), under fasting conditions, in two study periods with a wash-out of at least 3 days between the administrations, according to a randomised two-way, cross-over design.

10.1.3 Route and method of administration

Both T and R products will be orally administered in the morning of study Day 1, at 8:00±1 h, as follows:

- T: one film-coated tablet of IBA 600 mg film-coated tablet will be swallowed by the subject with 150 mL of still mineral water
- R: the entire content of one sachet of IBA 600 mg granules for oral solution will be dispersed in 100 mL of still mineral water until complete dissolution and drunk by the subject. Afterwards, the glass will be rinsed with a further 50 mL of still mineral water and the rinse drunk.

The Investigator will check that all subjects take the IMP appropriately.

10.1.4 Investigational product distribution

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

10.2 Packaging and labelling

The Sponsor will provide the Phase I Unit with 24 individual subject's kits and 12 reserve kits. Each kit will include a transparent zip bag containing 2 boxes, one for each study period. One box will contain 1 blister of 6 IBA 600 mg film-coated tablets, the other one 2 sachets of Espidifen® 600 mg granules for oral solution. The primary packaging of T will consist in a blister pack made by aluminium/polyethylene foil.

The products 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; 13), as follows:

a. Name, address and telephone number of the Sponsor, contract research organization or Investigator (the main contact for information on the product and clinical study)
b. Pharmaceutical dosage form, route of administration, quantity of dosage units, name/identifier and strength/potency
c. The batch and/or code number to identify the contents and packaging operation
d. A study reference code allowing identification of the study, site, Investigator and Sponsor if not given elsewhere
e. The study subject identification number
f. The name of the Investigator (if not included in (a) or (d))
g. Directions for use (refer to clinical study protocol)
h. "For clinical study use only" or similar wording
i. The storage conditions
j. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity
k. "Keep out of reach of children"

Labels will be in Italian.

10.3 Storage conditions

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

10.4 Drug accountability

The IMPs will be provided directly to the Investigator by the Sponsor, in excess of the amount necessary for the study (at least 50% excess).

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

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

11 INVESTIGATIONAL PLAN

11.1 Overall study design

This is a single centre, single dose, open-label, randomised, two-way, two-stage, cross-over bioequivalence study.

11.2 Discussion of design

The present study was designed taking into consideration the recommendations of the EMA "Guidance on the investigation of bioequivalence", CPMP/EWP/QWP/1401/98 Rev. 1 January 2010 (14) and the EMA "Ibuprofen oral use immediate release formulations 200-800 mg product-specific bioequivalence guidance" EMA/CHMP/356876/2017 (15).

The dose of IBA (600 mg) has been chosen since the aim of the Sponsor is to provide an alternative in tablet to the already approved IBA 600 mg sachet for oral solution. Since the recommended daily dose of IBA is 600-2400 mg (2), the selected dose respects the common therapeutic use.

Each randomised subject will be allocated to a sequence of treatment administrations in the two study periods (TR or RT) according to a computer-generated randomisation list (see § 15.1).

As foreseen by the EMA guideline (14), a cross-over design will be used to eliminate intra-subject variation in the comparison between the two formulations.

An open-label design was selected since the primary objective of the study is based on objective measurements of IBA active enantiomer in plasma and the outcome variables could not be influenced by the subjects or Investigator being aware of the administered products.

In view of the margin of uncertainty existing over a sample estimate to accomplish the study in terms of IBA PK, the study will be conducted according to a two-stage design. Details are given in § 17.2.

Blood sampling time-points and wash-out period (at least 3 days) were selected on the basis of the well-known ibuprofen PK profile, as reported in several previous clinical studies (7, 8, 9, 10, 11).

As concern the bioanalysis, a chiral method was chosen, since ibuprofen is a racemate and S-enantiomer is the active form of ibuprofen, predominant after oral administration of racemic compound (12). The bioequivalence test will be performed for the active ibuprofen S-enantiomer, to assess if an equivalent bioavailability in terms of rate (C_{max}) and extent (AUC_{0-t}) of absorption is obtained. In addition, the comparison of the bioavailability of the T versus R formulations will be assessed for ibuprofen R-enantiomer and for the sum of ibuprofen S-enantiomer and R-enantiomer. Moreover, a full evaluation of the PK profile of ibuprofen S-enantiomer and R-enantiomer will be performed.

This choice is in accordance with the EMA guideline (14), that reports “if one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer”.

12 STUDY POPULATION

12.1 Target population

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

12.2 Inclusion criteria

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

1. *Informed consent*: subjects able to complete and sign the informed consent before inclusion in the study
2. *Sex and Age*: men and women, 18-55 years old inclusive
3. *Body Mass Index*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 60-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study
6. *Contraception and fertility (women only)*: women of child-bearing potential must be using at least one of the following reliable methods of contraception:
    a. Hormonal oral, implantable, transdermal or injectable contraceptives for at least 2 months before the screening visit
    b. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
    c. A male sexual partner who agrees to use a male condom with spermicide
    d. A sterile sexual partner

    Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted.

    For all women, pregnancy test result must be negative at screening and Day -1.

12.3 Exclusion criteria

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

1. *Subjects*: subjects younger than 18 years or older than 55 years, subjects unable to give the informed consent, subjects with cognitive impairment and otherwise non-healthy subjects
2. *SARS-CoV-2 test:* positive Covid-19 Antigen Rapid Test at screening or Day -1
3. *Electrocardiogram (12-lead ECG in supine position)*: clinically significant abnormalities
4. *Physical findings:* clinically significant abnormal physical findings which could interfere with the objectives of the study

5. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
6. *Allergy*: ascertained or presumptive hypersensitivity to the active principle or formulations' ingredients or both; history of anaphylaxis to drugs or allergic reactions in general (in particular to NSAIDs), which the Investigator considers may affect the outcome of the study
7. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, immunological or neurological diseases that may interfere with the aim of the study
8. *Medications*: medications, including over the counter (OTC) medications, herbal remedies and vitamins, for 2 weeks before the start of the study. Hormonal contraceptives for women will be allowed
9. *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
10. *Blood donation*: blood donations for 3 months before this study
11. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
12. *Drug test*: positive result at the drug test at screening or Day -1
13. *Alcohol test*: positive alcohol test on Day -1
14. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
15. *Pregnancy (women only)*: positive or missing pregnancy test at screening or Day -1, pregnant or lactating women.

12.3.1 Not allowed treatments

No medication, including OTC, herbal remedies and vitamins, will be allowed for 2 weeks before the start of the study and during the whole study duration. Hormonal contraceptives for women will be allowed.

Paracetamol will be allowed as therapeutic countermeasure for AEs according to the Investigator's opinion.

The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the Investigator, together with the Sponsor, considers it could affect the study assessments or outcome.

13 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

13.1 Study visits and procedures

Each study subject will undergo 6 visits.

The study protocol foresees 2 periods separated by a wash-out interval of at least 3 days. Minimum study duration for each subject will be 6 days, screening visit included. A written informed consent will be obtained before any study assessment or procedure.

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

The following phases, visits and procedures will be performed:

- **Screening phase**
  - Screening – visit 1: between Day -21 and Day -2
  - Period 1 – visit 2: Day -1

- **Interventional phase**
  - Period 1 – visit 3: Day 1
  - Wash-out interval of at least 3 days between the two administrations
  - Period 2 – visit 4: Day -1
  - Period 2 – visit 5: Day 1

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

		Day	Procedures/Assessments	Notes
Screening	**Visit 1**	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Covid-19 Antigen Rapid Test ➢ Drug screening test ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, physical abnormalities) ➢ Vital signs (blood pressure, heart rate) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urinalysis, virology ➢ Serum pregnancy test (women only) ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ AEs monitoring	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source documents only and will not be transferred to the Sponsor
Period 1	**Visit 2**	*Day -1*	➢ Covid-19 Antigen Rapid Test ➢ Alcohol test ➢ Vital signs (blood pressure, heart rate) ➢ Urine pregnancy test (women only) ➢ Drug screening test ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomisation (e.g., 001, 002, etc.) ➢ AEs and concomitant medications	Arrival at the Phase I Unit in the evening Confinement until the evening of Day 1 Standardised dinner Fasting overnight for at least 10 h
	Visit 3	*Day 1*	➢ IMP administration at 08:00±1h ➢ Blood sample collection for PK analysis at: pre-dose (0), 5, 10, 20, 30, 40, 50 min and 1, 1.5, 2, 3, 4, 6, 9, 12 h post-dose ➢ Vital signs (blood pressure, heart rate) at 12 h post-dose ➢ AEs and concomitant medications	All subjects will be fasting for 5 h post-dose Standardised lunch at approximately 5 h post-dose Discharge from the Phase I Unit in the evening, after the 12 h post-dose blood sample collection and vital signs check. Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions
Wash-out		*At least 3 days*	➢ A wash-out interval of at least 3 days will elapse between the two administrations of Periods 1 and 2	

		Day	Procedures/Assessments	Notes
Period 2	**Visit 4**	*Day -1*	➢ As Visit 2 with the exception of inclusion/exclusion criteria, eligibility evaluation, enrolment and randomisation	
	Visit 5	*Day 1*	➢ As Visit 3	
Final visit/ETV		*Day 1 of period 2 or ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ Vital signs (blood pressure, heart rate) (ETV only) ➢ Laboratory analyses as at screening, with the exception of virology and pregnancy test ➢ AEs and concomitant medications In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reaction

13.2 Diet and lifestyle

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

On Day 1 of each study period, the subjects will remain fasted until 5 h post-dose. Standardised lunch will be served at approximately 5 h post-dose.

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

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

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

13.2.1 Restrictions

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

During confinement, the subjects will not take any food or drinks, except water, apart from the standardised meals.

For the 4 h following the administration, when not involved in study activities, the subjects will remain seated. They will not be allowed to lie down.

Hazardous, strenuous or athletic activities will not be permitted.

14 DESCRIPTION OF SPECIFIC PROCEDURES

14.1 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 § 18), 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).

14.1.1 Body weight and BMI

Body weight will be recorded at screening and final visit/ETV.

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

14.1.2 Vital signs

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

- Screening visit
- On Day -1 of each study period
- On Day 1 at 12 h post-dose of each study period (the 12 h measurement on Day 1 of Period 2 will correspond to the final assessment)
- ETV

14.1.3 ECGs

12-Leads ECGs will be performed (in supine position) at screening only.

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

14.2 Clinical laboratory assays

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

HAEMATOLOGY
Leukocytes and leukocyte differential count, erythrocytes, haemoglobin, haematocrit, MCV, MCH, MCHC, thrombocytes.

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

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

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

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

A Covid-19 Antigen Rapid Test will be performed at screening, immediately after the informed consent signature, and on Day -1 of each study period.

A urine drug screening test will be performed at the Phase I Unit at screening and on Day -1 of each study period.

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

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

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

14.3 Sampling for PK analysis

14.3.1 Venous blood sampling

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

- pre-dose (0), 5, 10, 20, 30, 40, 50 min and 1, 1.5, 2, 3, 4, 6, 9, 12 h post-dose

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

Table 14.3.1.1 Tolerance ranges for the scheduled sampling times

Sampling time	Tolerance range
Pre-dose (0)	Within 30 minutes before IMP administration
0.08 h (5 min), 0.17 h (10 min)	0 min
0.33 h (20 min), 0.50 h (30 min)	± 1 min
0.67 h (40 min), 0.83 h (50 min)	± 2 min
1, 1.5 h	± 3 min
2, 3, 4 h	± 5 min
6, 9, 12 h	± 10 min

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

The remaining 8 mL will be collected from the catheter and transferred with a syringe into EDTA K_2 tubes.

The samples will be centrifuged at 1900 g (± 38 g) for at least 10 min at 4 °C (± 4 ºC) to obtain plasma. The time between blood collection and placement in the centrifuge cannot exceed 60 minutes. Each plasma sample will be immediately divided into 3 aliquots, P1 (1.0 mL), P2 (1.0 mL) and P3 (the remaining amount), in pre-labelled polypropylene tubes, and stored frozen at -20 ºC (± 5 ºC) until analyses. The time between the end of centrifugation and aliquot storage cannot exceed 181 minutes.

If any clinical assessment, such as vital signs measurement, 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 can be influenced by the blood sampling. Therefore, this assessment can be performed within 30 min before the scheduled PK time-points (see table below). Any deviations outside the recommended time will be verified through DCFs.

Table 14.3.1.2 Tolerance ranges for the safety assessments in relation to blood sampling times

Vital signs sampling time	Vital signs tolerance range
12 h post-dose	Within 30 minutes before blood sampling

However, since vital signs measurements will be performed for safety reasons only, deviations from the planned time schedule will be considered not relevant.

14.3.2 Analytics

The concentration of ibuprofen S-enantiomer and R-enantiomer will be determined in plasma samples at Anapharm Europe S.L.U., Spain, using a fully validated chiral LC-MS/MS method.

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

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

14.3.3 Labelling, storage and transport of samples

14.3.3.1 Samples labelling

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

Study code	Study CRO-PK-22-360 - Sponsor code Z7100J02
Subject number	001/002/003/etc.
Tube identification	P1/P2/P3
Period	1/2
Scheduled sampling time	as min or h; see Table 14.3.1.1 and § 14.3.1

14.3.3.2 Samples storage and transport

During the study the samples will be stored at -20 ºC (± 5 ºC). At the end of each collection day, P1 / P3 and P2 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 S.A. Phase I Unit, Switzerland, to the analytical laboratory, Anapharm Europe, S.L.U., Spain. All aliquots will remain stored at the analytical laboratory for 3 months after the finalisation of the bioanalytical report.
After that period, the Sponsor will decide to either destroy or return or store the aliquots for an extended period under applicable fees as specified in the bioanalytical contract or service agreement.

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

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

No analyses different from those stated in this protocol and agreed by the subjects when signing the informed consent form will be performed unless a new informed consent and a new approval from the Ethical Committee is obtained. The subjects may ask to destroy their own samples at any time.

14.4 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:

30 samples x 10 mL = 300 mL

In total 325 mL of blood (not exceeding a normal blood donation) will be withdrawn from each subject.

15 ASSIGNMENT OF STUDY TREATMENT

15.1 Randomisation

The randomisation list will be computer-generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of SAS® version 9.3 (TS1M1) (18) or higher (the actual version will be stated in the final report). The randomisation list will be supplied to Sponsor to prepare the Subject's kits. The randomisation list will be attached to the final clinical study report (CSR).

15.2 Treatment allocation

Subjects will be assigned to one of the two sequences of the two treatments (T/R; R/T) according to the randomisation list and to the 2-way cross-over design.
The 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.

15.3 Blinding

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

16 EVALUATION PARAMETERS

16.1 Study variables/endpoints

16.1.1 Primary variables/endpoints

- C_{max} and AUC_{0-t} of plasma ibuprofen S-enantiomer after single oral dose of T and R products

16.1.2 Secondary variables/endpoints

- t_{max}, F_{rel} and, if feasible, $\%AUC_{extra}$, $AUC_{0-\infty}$, $t_{1/2}$ and λ_Z of plasma ibuprofen S-enantiomer after single oral dose of T and R products
- C_{max}, AUC_{0-t}, t_{max}, F_{rel} and, if feasible, $\%AUC_{extra}$, $AUC_{0-\infty}$, $t_{1/2}$ and λ_Z of plasma ibuprofen R-enantiomer after single oral dose of T and R products
- C_{max}, AUC_{0-t}, t_{max}, F_{rel} and, if feasible, $\%AUC_{extra}$, $AUC_{0-\infty}$, $t_{1/2}$ and λ_Z of total ibuprofen, calculated as the sum of ibuprofen S-enantiomer and R-enantiomer concentrations, after single oral dose of T and R products
- TEAEs, vital signs (blood pressure, heart rate), physical examinations, body weight, clinical laboratory parameters.

16.2 PK assessments

The following PK parameters will be measured and/or calculated for plasma ibuprofen S-enantiomer, plasma ibuprofen R-enantiomer and total ibuprofen (calculated as the sum of the two enantiomers plasma concentrations), using the validated software Phoenix WinNonlin® version 6.3 (17) or higher (the actual version will be stated in the final report):

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

F_{rel}: Relative bioavailability, calculated as ratio AUC_{0-t} (T)/AUC_{0-t} (R)

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).

16.3 Safety assessments

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

17 STATISTICAL METHODS

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

Not available data will be evaluated as "missing values". The analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (18) or higher (the actual versions will be stated in the CSR).
The statistical analysis of PK parameters will be performed using Phoenix WinNonlin® version 6.3 (17) or higher and SAS® version 9.3 (TS1M1) or higher (18).

17.1 Analysis Sets

17.1.1 Definitions

A subject will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.

A subject will be defined as eligible if he/she meets all the inclusion/exclusion criteria. Otherwise, he will be defined as a screen failure.

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

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

The following analysis sets will be defined:

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

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

17.1.2 Reasons for exclusion from the PK sets before bioanalysis

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

- vomiting and diarrhoea after drug intake which could render the plasma concentration-time profile unreliable
- intake of concomitant medications which could render the plasma concentration-time profile unreliable
- AEs which could render the plasma concentration-time profile unreliable
- administration errors which could render the plasma concentration-time profile unreliable
- other events which could render the plasma concentration-time profile unreliable

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

17.1.3 Reasons for exclusion from the PK sets after bioanalysis

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

- subjects with lack of any measurable concentrations or only very low plasma concentrations for R product. A subject is considered to have very low plasma concentrations if his/her AUC is less than 5% of the R product 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 R 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 $AUC_{0-\infty}$.

17.2 Sample size and power considerations

The study will be conducted according to a two-stage design.

24 men and women will be enrolled in study stage 1. No drop out replacement is foreseen. After the end of stage 1, PK parameters will be calculated and an ad interim bioequivalence test will be performed on ibuprofen S-enantiomer C_{max} and AUC_{0-t}. To safeguard the overall type I error, the one-sided α-level of the bioequivalence test will be set to 0.0294 according to the Pocock spending function.
Should bioequivalence be proven with the results of the first stage, the primary objective of the study will be satisfied and the second study stage will not take place.
Should bioequivalence not be proven with the results of stage 1 and with an *a posteriori* calculated power ≥ 80% for AUC_{0-t} or C_{max}, the study will be stopped without proving bioequivalence.

Should bioequivalence not be proven with the results of the first stage and with an *a posteriori* calculated power < 80% for both AUC_{0-t} and $C_{max,}$ the overall sample size for the study (stage 1 + stage 2) will be calculated on the basis of the point estimate of the T/R ratio of the geometric means of 0.95 and of the variance of stage 1.
The additional subjects will be enrolled in study stage 2. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of both study stages.

17.3 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.

17.4 Analysis of PK parameters

17.4.1 Descriptive PK

A descriptive PK will be presented for ibuprofen S-enantiomer, ibuprofen R-enantiomer and total ibuprofen. The total ibuprofen concentrations will be calculated by the CRO Biometry Unit as the sum of ibuprofen S-enantiomer and R-enantiomer concentrations. 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).

17.4.2 Statistical comparison of PK parameters

According to the current European Guideline on the Investigation of Bioequivalence (14), PK parameters AUC_{0-t} and C_{max} for ibuprofen S-enantiomer, ibuprofen R-enantiomer and total ibuprofen will be analysed using analysis of variance (ANOVA). Before analysis, the data will be transformed using a neperian logarithmic transformation. ANOVA will be performed on the data from study stage 1 and, if necessary, on the combined data from stage 1 and stage 2. Treatment, period, sequence, subject (sequence) will be taken into account as sources of variation during the analysis on the data from stage 1. During the analysis on the combined data from stage 1 and stage 2 (if any), stage, treatment, period (stage), sequence, sequence*stage, subject (sequence*stage) will be taken in account as sources of variation.

For both the analysis (stage 1 data) and the final combined analysis (stage 1 and 2 data, if any), acceptance criterion for bioequivalence is that the two-sided 94.12% confidence interval of the T/R ratio of the least-square geometric means of the parameters is within the 80.00-125.00% range, according to the Pocock α spending function.

T_{max} will be analysed using the non-parametric Wilcoxon signed-rank test.

17.5 Safety and tolerability evaluation

17.5.1 Adverse events

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

- PTAEs: all AEs occurring before the first dose of IMP
- TEAEs: all AEs occurring 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.

17.5.2 Physical examination

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

17.5.3 Laboratory data

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

17.5.4 Vital signs

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

17.5.5 Body weight

Body weight values at screening and final visit/ETV will be listed and summarised by descriptive statistics.

18 DEFINITION AND HANDLING OF AEs AND SAEs

18.1 Applicable SOPs

AEs definition, classification and management will follow the Sponsor's SOPs. The AE form present in the CRF and the SAE form will also follow the Sponsor SOPs.

The full SOP and/or a Safety Management Plan will be made available to the Phase I Unit.

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

18.2 Definition of Adverse Event (AE)

An AE is "*any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention*".

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

AEs include:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

AEs does not include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

18.3 Definition of Adverse Drug Reaction (ADR)

An ADR is "*any untoward and unintended response to a medicinal product related to any dose administered".*
All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as AEs. The expression reasonable causal relationship means to convey in general that there is evidence or matter to suggest a causal relationship.

- **Unexpected ADR**:

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

- **Reference Safety Information (RSI)**: in order to assess whether an ADR is expected, the Summary of Product Characteristics (SmPC) for R product and the IB (2) for T product (section "*Summary of Data and Guidance for the Investigator*" or a new section, as applicable) will be used.

18.4 Definition of Serious Adverse Events or Serious Adverse Drug Reaction

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

- results in death
- is life-threatening (i.e., the term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was 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 were more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity (i.e., the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma which may interfere with or prevent everyday life functions but do not constitute a substantial disruption)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but, according to appropriate medical judgment, it may jeopardize the subject's health status and may require intervention to prevent any of the outcomes

listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

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

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an ADR that is both unexpected (not consistent with the RSI) and also meets the definition of a SAE.

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

18.5 Definition of Severity of Adverse Events

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: an event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: an event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

18.6 Definition of Adverse Event causality

Causality shall be determined according to the definition of ADR given in 18.3.

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The Investigator will also consult the IB and/or SmPC for marketed products, in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All AE judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as adverse reactions. The causality assessment given by the Investigator should not be downgraded by the Sponsor.

The following binary decision for causality will be used:

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

Features supportive of an association include:

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

18.7 Adverse Events recording

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

18.8 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: final visit/ETV

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

18.9 Adverse Events reporting

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

The Investigator must report all AEs which occur during the study, regardless of their relationship to the IMP.

18.10 SAEs reporting

The Investigator must report the SAEs immediately and not later than 24 h from when he becomes aware of the SAE, by faxing the "Serious Adverse Event Form" (back up plan) or e-mailing as scanned attachment (backup plan) or by Electronic Data Capture to the Drug Safety Unit (DSU) personnel of Zambon (preferred method).

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

Another copy of the "Serious Adverse Event Form" will be retained by the Investigator for the Investigator's file.

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

If outside the window established in the protocol the Investigator becomes aware of a SAE, it is the Investigator's responsibility to report the SAE. The Investigator might use the "Serious Adverse Event Form" via email or fax, but the SAE must not to be reported in the CRF, as it is not an event occurred within the study period.

18.11 Follow-up for Adverse Events

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

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

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

18.12 SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the Sponsor (day 0).
For fatal and life-threatening SUSARs the EC and Competent Authority (Swissmedic) should be informed as soon as possible and in any case within 7 days.

If the initial report is incomplete, e.g. not all the information/assessments were available, a complete report should be sent within an additional 8 days. Complete follow-up report should be sent within 15 calendar days.

SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

The minimum information to be reported includes:

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

In addition, in order to properly process the report electronically, the following administrative information should be provided:

- the sender's (case) safety report unique identifier,
- the receipt date of the initial information from the primary source,
- the receipt date of the most recent information,
- the worldwide unique case identification number,
- the sender identifier.

18.13 Other events qualified for expedited reporting

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

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

  – a SAE which could be associated with the study procedures and which could modify the conduct of the study
  – a significant hazard to the subject population such as lack of efficacy of a medicinal product used for the treatment of a life-threatening disease
  – a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical study.

18.14 SAEs: contacts

The Phase I Unit 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 Investigator contact for SAEs is the following:

Dr. Milko Radicioni
Phone: +41.91.64.04.450
Fax: +41.91.64.04.451
Email: milko.radicioni@croalliance.com

The Investigator will report any SAE to the Sponsor. The Sponsor's details for SAEs are the following:
Phone: +39.02.66.524.444
Fax: +39.02.66.524.038
Email: drugsafety@zambongroup.com

18.15 Pregnancy

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

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

If pregnancy results in abnormal outcome that the investigator considers to be due to the IMP, this will be treated as an expedited ADR report.

19 SUBJECTS' DISCONTINUATION, STUDY TERMINATION

19.1 Withdrawal of subjects

If, for a subject, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

19.1.1 Primary reason for discontinuation

Primary reason for discontinuation from the study could be one of the following:

- **Adverse event**: Any (significant) AE that in the opinion of the Investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 18.2.
- **death**
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**
- **protocol deviation**: an event or decision that stands in contrast to the 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

19.1.2 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

Subjects withdrawn from the study will not be replaced.

19.2 Study termination

The study will be considered terminated at the date of the LSLV 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 technical or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation must be documented appropriately. In this event, no further subjects will be treated with the IMPs, and subjects already treated will undergo all safety assessments, as planned.

20 DATA MANAGEMENT PROCEDURES

20.1 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 must be dated and initialled. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. The Investigator must provide a reasonable explanation for all missing data.
The CRFs will be completed, signed by the Investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the Sponsor.

20.2 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., Z7100J02), the 3-digit site number (i.e. 001), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, 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 (randomised 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 randomised subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the CSR and will be used to identify the subjects in in-text tables or wording (if applicable).

20.3 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.

20.3.1 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.

21 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

21.1 Monitoring

The monitoring visits will be conducted by the appointed study CRA (§ 7.6) according to CROSS Research SOPs.

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.

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.

21.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments/modifications, ICH-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOA++ principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete-Consistent-Enduring-Available-Traceable).

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

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

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

21.3 Applicable SOPs

The Sponsor and the CRO will follow their respective SOPs in the conduct of the respective activities as specified in the signed assignment of responsibilities. For definition and handling of AEs the Sponsor's SOP will be used. SOPs will be made available for review, if required.

21.4 Data access

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

21.5 Audits and inspections

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

The study may also be inspected by regulatory authorities.

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

22 ETHICAL CONSIDERATIONS

22.1 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.

22.2 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 IMPs and treatment procedures, as applicable)
- any potential negative effects attributable to the study product or treatment
- the freedom to ask for further information at any time
- the subjects' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of a subject insurance cover and obligations following from this cover

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

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

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the Investigator's study file according to the regulatory requirements (see § 23.3).
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.

22.3 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 Swiss Health Authorities.

23 ADMINISTRATIVE PROCEDURES

23.1 Material supplied to the clinical centre

Beside the 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 the IB for the test product and the SmPC for the reference product
- informed consent forms

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

23.2 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 submitted to the concerned Regulatory Authorities, as applicable. The amendments will be applicable only after approval unless the changes consist of urgent safety measures to protect study subjects.

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

23.3 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 stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.

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

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

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

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

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

23.4 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.

23.5 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.

In this Phase I study the CRO plays the role usually performed by the clinical centre (§ 7.2 and § 7.5), performing services like clinical monitoring and related drafting of monitoring reports; reporting and project management; statistics; drug/samples storage and trial document archiving directly or availing itself of authorised third parties.
Data on subjects collected in the CRFs during the study will be documented in a coded way (§ 20.2). 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.

With reference to EU Regulation number 679/2016 of European Parliament and of the Council of 27 April 2016, the General Data Protection Regulation (GDPR), such as Swiss Federal Data Protection Act of 19 June 1992 and other local law provisions the data protection roles within the present Phase I study are the following:

- The Sponsor and the CRO (that plays the role of the clinical centre in this Phase I study; § 7.2 and § 7.5) are Joint Controllers. The data processing activities performed within the Phase I clinical trial are jointly designed, addressed and managed by the Parties, pursuant to Article 26 of General Data Protection Regulation (EU) 2016/679 on personal data protection (hereinafter the "GDPR"). The Joint Controllers will process the personal and study data of the participants exclusively for study related purposes and for pharmacovigilance purposes or for other legitimate purposes.
- The Principal Investigator will process the data as a Data Processor, on behalf of the CRO.

As concerns the data protection information/notice, participants must be informed properly about all the data protection elements provided by articles 13 and 14 of GDPR and similar provisions of the Swiss Federal Data Protection Act of 19 June 1992 and subsequent amendments. Investigator or his/her representative will give to the participant a proper data protection information notice compliant with GDPR and will consequently ask the participant for a data protection consent, together with the study informed consent. According to the provisions of the GDPR and Swiss Data Protection Law, the level of disclosure in the informed consent must also be explained to the participant. The participant must be informed that his/her medical records may be examined by Auditors or other authorised personnel appointed by the Sponsor, by appropriate EC members and by inspectors from regulatory authorities.

As regards the organisational and security measures adopted, the operations of collection, storage, circulation of biological samples as well as all the data processing operations regarding the study data are performed in compliance with GDPR and Swiss Data Protection Law. The Investigator or his/her representative will assign to the participants a unique identifier. The Investigator will be the only one who can match the participant's identity with the data referred to the study. Any participants' records or datasets that are transferred to the Sponsor will contain the identifier code only; participants' names or any other information which would make them identifiable will not be transferred to the Sponsor.

23.6 Publication policy

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

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

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

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

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