16. APPENDICES

16.1 Study information

16.1.1 Protocol and protocol amendments

The following documents are enclosed:

- Clinical study protocol, Final version 1.0, 28JUL14
- Protocol amendment No. 1, Final version 2.0, 25NOV14

Study protocol CRO-PK-14-288 - Sponsor code KSL0114

Two-way crossover, randomised, single dose and two-stage bioequivalence phase I study of ketoprofen lysine salt as immediate release tablets formulation (40 mg) versus ketoprofen lysine salt as granules for oral solution (80 mg bipartite sachet, half sachet) after oral administration to healthy volunteers of both sexes

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

Test formulation:	Ketoprofen lysine salt (KLS), immediate release tablets 40 mg, corresponding to 25 mg as ketoprofen, Dompé s.p.a., Italy
Reference formulation:	OKi® 80 mg granules for oral solution (bipartite sachet), half sachet containing 40 mg of KLS corresponding to 25 mg as ketoprofen, Dompé s.p.a., Italy
Sponsor:	Dompé s.p.a. Via Campo di Pile, 67100 L'Aquila Milan offices: Via Santa Lucia 6, 20122 Milano - Italy Phone: +39.02.58383.1 Fax: +39.02.58383.324 Email: mauro.ferrari@dompe.it
Investigators:	Milko Radicioni, MD - Principal investigator Antonio Rusca, MD, FMH - Co-investigator CROSS Research S.A., Phase I Unit, Via F.A. Giorgioli 14 CH-6864 Arzo, Switzerland Phone: +41.91.63.00.510 Fax: +41.91.63.00.511 Email: clinic@croalliance.com
Development phase:	I
Version and date:	Final version 1.0, 28JUL14

This study will be conducted in accordance with Good Clinical Practice (GCP), ICH topic E6

This document comprises 59 pages

PROTOCOL APPROVAL

SPONSOR
Dompé s.p.a., Italy

Clinical Development Manager
Mauro Paolo. Ferrari, PharmD

28th JULY 2014 _____
Date Signature

Research & Development Director
Marcello Allegretti, ChemD

30/07/2014 _____
Date Signature

INVESTIGATOR

Principal investigator
I have read this protocol and agree to conduct this study in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

Milko Radicioni, MD
Cross Research Phase I Unit, Switzerland

29 JUL 2014 _____ _____
Date Signature

CRO
CROSS S.A., Switzerland, and its affiliated companies CROSS Research S.A. and CROSS Metrics S.A.

Coordination
Angelo Vaccani, PhD, Clinical Project Leader

28 JUL 2014 — Angelo Vaccani
Date — Signature

Pharmacokinetic Analysis
Luca Loprete, MSc, Senior Pharmacokineticist

28 JUL 2014 — Luca Loprete
Date — Signature

Biometry Unit Representative
Matteo Rossini, MSc, Biometry Manager, Unit Head

28 JUL 2014 — Matteo Rossini
Date — Signature

Quality Assurance Unit Representative
Maurizio Cuocolo, PharmD, Quality Assurance

28 JUL 2014 — Maurizio Cuocolo
Date — Signature

STUDY SYNOPSIS

Title: Two-way crossover, randomised, single-dose and two-stage bioequivalence phase I study of ketoprofen lysine salt as immediate release tablets formulation (40 mg) versus ketoprofen lysine salt as granules for oral solution (80 mg bipartite sachet, half sachet) after oral administration to healthy volunteers of both sexes
Protocol number: CRO-PK-14-288 - Sponsor study code KSL0114
Clinical phase: Phase I
Study design: Single centre, single-dose, open, randomised, two-way cross-over, two-stage bioequivalence study
Planned nr. of centres / countries: 1/Switzerland
Sponsor: Dompé s.p.a. Via Campo di Pile, 67100 L'Aquila Milan offices: Via Santa Lucia 6, 20122 Milano - Italy
Investigator and centre: *Principal Investigator*: Milko Radicioni, MD; *Co-Investigator*: Antonio Rusca, MD, FMH; Cross Research Phase I Unit, Via F. A. Giorgioli 14 CH-6864 Arzo, Switzerland
Investigational product(s): TEST (T): Ketoprofen lysine salt (KLS), immediate release tablets 40 mg, corresponding to 25 mg as ketoprofen, Dompé s.p.a., Italy REFERENCE (R): OKi®, 80 mg granules for oral solution (bipartite sachets), each half sachet containing 40 mg of KLS corresponding to 25 mg as ketoprofen, Dompé s.p.a., Italy
Dose regimen: A single oral dose (40 mg) of each formulation (test and reference) will be administered to healthy volunteers under fasting conditions in two consecutive study periods with a wash-out interval of at least 4 days between the two administrations.
Objective: To investigate the bioequivalence between two formulations containing ketoprofen lysine salt (KLS) when administered as single oral dose in two consecutive study periods to healthy male and female volunteers under fasting conditions.
End-points: **Primary end-point:** to evaluate the bioequivalent rate (C_{max}) and extent (AUC_{0-t}) of absorption of ketoprofen after single dose administration of test and reference. **Secondary end-points:** ➢ to describe the pharmacokinetic (PK) profile of ketoprofen after single dose administration of test and reference; ➢ to collect safety and tolerability data after single dose administration of test and reference.
Study variables: **Primary variables**: C_{max} and AUC_{0-t} of ketoprofen calculated from plasma concentrations after single oral dose of test and reference. **Secondary variables:** ➢ $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, λ_z and F_{rel} of ketoprofen calculated from plasma concentrations after single oral dose of test and reference; ➢ Treatment-emergent AEs (TEAEs), vital signs (BP, PR, BT), body weight, ECG, laboratory parameters
Analytics: Ketoprofen free acid will be determined in plasma by a HPLC-UV validated assay at Dompé Bioanalytical Laboratories, L'Aquila, Italy. Analytical facilities and procedures are in compliance with GLP regulations.
Safety and tolerability assessments: Treatment-emergent adverse events (TEAEs); vital signs (blood pressure [BP], pulse rate [PR], body temperature [BT]), body weight, physical examinations; laboratory tests performed at screening and final visit/early termination visit (ETV); electrocardiogram (ECG) at screening and final visit/ETV

STUDY SYNOPSIS (cont.)

Sample size: in a first study stage 30 healthy volunteers (at least 12 subjects per sex) will be included and treated receiving test and reference treatment according to the cross-over design. Drop-out subjects will not be replaced. After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should bioequivalence be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power of at least 80%, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage or should it be proven with an *a posteriori* calculated power lower than 80%, the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. The Sponsor will decide whether the study has to continue or not. In the first case, the additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages. The second stage will be performed after notification of the sample size to the local Ethics Committee and to the central Swiss authority (Swissmedic).

Main selection criteria:

Inclusion criteria:

1. *Informed consent:* signed written informed consent before inclusion in the study
2. *Sex and Age:* males/females, 18-55 years old inclusive
3. *Body Mass Index (BMI):* 18.5-30 kg/m^2 inclusive
4. *Vital signs:* systolic blood pressure (SBP) 100-139 mmHg, diastolic blood pressure (DBP) 50-89 mmHg, pulse rate (PR) 50-90 bpm and body temperature (BT) ≤ 37.5° C, measured after 5 min of 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 (females only)*: females of child-bearing potential and with an active sexual life 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 [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   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 female subjects, pregnancy test result must be negative at screening.

Exclusion criteria:

1. *Electrocardiogram (ECG 12-leads, supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principles (ketoprofen) and/or formulations' ingredients; history of hypersensitivity to drugs (in particular to NSAIDs) or allergic reactions in general, which the Investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory (including asthma), skin, haematological, endocrine or neurological and autoimmune diseases that may interfere with the aim of the study
6. *Medications*: medications, including over the counter (OTC) drugs [in particular ketoprofen and acetylsalicylic acid (ASA), and NSAIDs in general], herbal remedies and food supplements taken 2 weeks before the start of the study. Hormonal contraceptives for females will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study (date of the informed consent signature)

STUDY SYNOPSIS (cont.)

Exclusion criteria (cont.):

8. *Blood donation*: blood donations for 3 months before this study
9. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [> 1 drink/day for females and > 2 drinks/day for males, defined according to the USDA Dietary Guidelines 2010 (6)], caffeine (> 5 cups coffee/tea/day) or tobacco abuse (≥ 6 cigarettes/day)
10. *Drug test*: positive result at the drug test at screening
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (< 1600 or > 3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

Schedule:

Visit	Day	Procedures/Assessments	Notes
Screening – visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urine analysis, serum virology and serum pregnancy test (females only) ➢ Urine multi-drug kit test ➢ AE monitoring ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the clinical centre source document only and will not be transferred to the sponsor
Visit 2	*Day -1*	➢ Alcohol breath test ➢ Vital signs measurement ➢ Urine pregnancy test (females only) ➢ AE and concomitant medications ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and Randomisation	Arrival at the clinical centre in the evening Confinement until the evening of day 1 Standardised low-fat dinner Fasting for at least 10 h (overnight)
Visit 3	*Day 1*	➢ IMP administration: 8:00 ± 1h ➢ Vital signs measurement: 8h post-dose ➢ Blood sample collection for PK analysis: pre-dose (0), 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6 and 8 h post-dose ➢ AE and concomitant medications	<u>Day 1</u> Standardised lunch at 13:00 (5 h post-dose) Discharge from the clinical centre in the evening after the 8 h blood sample collection and vital signs check

STUDY SYNOPSIS (cont.)

Schedule (cont.):

Wash-out	*At least 4 days*	A wash-out interval of at least 4 days between the two administrations of the two study periods	
Visit 4	*Day -1*	As visit 2, with the exclusion of Inclusion/exclusion criteria evaluation, Eligibility evaluation, Enrolment and Randomisation	Arrival at the clinical centre in the evening Confinement until the evening of day 1 Standardised low-fat dinner Fasting for at least 10 h (overnight)
Visit 5	*Day 1*	As visit 3. Test or reference IMP administered according to the randomisation list and cross-over design	<u>Day 1</u> Standardised lunch at 13:00 (5 h post-dose) Final discharge from the clinical centre after the 8 h blood sample collection and final visit
Final Visit/ETV	*Day 1 of period 2 / at ETV in case of discontinuation*	➢ Full physical examination (body weight, physical abnormalities and, in case of ETV, vital signs) ➢ ECG recording ➢ Laboratory analyses as at screening, with the exception of serum virology, urine drug test and pregnancy test ➢ AE and concomitant medications In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

During confinement, the subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before IMP administration. Water will be allowed as desired, except for one h before and two h after IMP administration. In order to maintain an adequate hydration, the subjects will be encouraged to drink at least 180 mL of mineral water every 2 h for 6 h post-dose, starting at 2 h post-dose. In the evening of day -1, the subjects will receive a standardised light and low-fat dinner. 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.
Coffee, tea and any other food containing xanthines (i.e. coke, chocolate, etc.) will be forbidden during confinement. Alcohol and grapefruit will be forbidden from 48 h before the first administration until the end of the study. During confinement, routine ambulant daily activities will be strongly recommended.
The subjects will be allowed to smoke not more than 1 cigarette after lunch.

STUDY SYNOPSIS (cont.)

Data analysis:
The PK analysis and the statistical analysis of PK parameters will be performed using Phoenix WinNonlin® version 6.3 or higher, Pharsight Corporation and SAS® version 9.3 (TS1M1) or higher. The statistical analysis of safety data will be performed using SAS® version 9.3 (TS1M1) for Windows or higher. C_{max} and AUC will be compared between T and R using analysis of variance (ANOVA) for a cross-over design on log-transformed data. ANOVA will be performed on the data from stage 1 and, if applicable, the combined data from stage 1 and stage 2. The statistical analysis will take into account treatment, period, sequence and subject (sequence) as source of variation in the first stage. If the analysis of combined data from the two stages is required, stage, treatment, period (stage), sequence, sequence*stage and subject (sequence*stage), will be taken into account as source of variation. Acceptance criterion for bioequivalence is a 94.12% confidence interval for the T/R ratio of the geometric means of the parameters under consideration within the 80.00-125.00% range, according to the current guidelines for bioequivalence studies and to the Pocock α spending function. t_{max} will be analysed using the non-parametric Friedman test. The data documented in this trial and the measured clinical parameters will be described using classic descriptive statistics for quantitative variables and frequencies for qualitative variables

Timing:
EC meeting: 26AUG14; planned clinical phase: NOV14; planned reporting: 25 working days after availability of analytical results

STUDY SCHEDULE

ACTIVITIES	Screening	PERIOD 1, 2 (wash-out at least 4 days)		
Visit	**V1**	**V2, V4**	**V3, V5**	**Final/Early Termination Visit (ETV)[8]**
	Days -14/-2	**Day -1**	**Day 1**	
Informed consent	x			
Demography	x			
Lifestyle	x			
Medical history and underlying disease	x			
Physical abnormalities	x			x
Previous and concomitant treatments	x	x	x	x
Height	x			
Body weight	x			x
Alcohol breath test		x		
Laboratory analysis[1]	x			x
Virology	x			
Drug screening	x			
BP, PR, BT	x	x	x[2]	x[2]
Pregnancy test[3]	x	x		
ECG	x			x
Inclusion/exclusion criteria evaluation	x	x[9]		
Eligibility evaluation	x	x[9]		
Enrolment and Randomisation		x[9]		
Confinement		x		
Discharge			x	
Drug administration[4]			x	
Blood samplings[5]			x	
Standardised meals[6]		x	x	
AEs monitoring[7]	x	x	x	x

1. Full laboratory analysis will be performed at screening visit. The same analysis will be performed at final visit with the exclusion of virology, drug screening and serum pregnancy test
2. at 8 h post-dose, corresponding to the final visit assessment at the end of period 2; at early termination visit (if applicable)
3. Females only. Serum β-HCG test at screening visit; urine test at the clinical centre on day -1 of each study period
4. at 8:00 ± 1 h
5. Pre-dose (0), 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6 and 8 h post-dose
6. Standardised meal will be served at approximately 5 h after the 1st drug administration. A standardised light and low-fat dinner will be served on day -1 of each period
7. AEs will be monitored from the screening visit, immediately after informed consent, up to the final visit.
8. on day 1 of period 2, after the 8 h blood sampling and vital signs check, subjects will undergo a final visit. In case of discontinuation, subjects will undergo an ETV
9. On visit 2 only

TABLE OF CONTENTS

TABLES

LIST OF ABBREVIATIONS

β-HCG	human chorionic gonadotropin β
γ-GT	γ-Glutamyl transpeptidase
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOA	Attributable-Legible-Contemporaneous-Original-Accurate
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from time zero to time t
$AUC_{0-\infty}$	Area under the concentration vs. time curve up to infinity
BE	Bioequivalence
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
BT	Body temperature
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
C_{max}	Peak drug concentration
CMS	Clinical Medical Service
CPL	Clinical Project Leader
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CRS	Clinical Study Report
CS	Clinically Significant
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
ETV	Early Termination Visit
F_{rel}	Relative Bioavailability
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
KLS	Ketoprofen lysine salt
HBs Ag	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibodies
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IUD	Intra-Uterine Device
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
MW	Molecular Weight
N	Normal

NA	Not Applicable
NC	Not calculated
NCS	Not clinically significant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
PE	Point Estimate
PK	Pharmacokinetics
PR	Pulse Rate
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R	Reference
RBC	Red Blood Cells
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test
TEAE	Treatment-Emergent Adverse Event
THC	delta-9-tetrahydrocannabinol
$t_{1/2}$	Half-life
T_{max}	Time to achieve C_{max}
USDA	United States Department of Agriculture
WBC	White Blood Cells
WHODDE	World Health Organisation Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

NSAIDs are a chemically heterogeneous group of compounds, often chemically unrelated, which share some therapeutic actions and adverse events. The principal therapeutic effects of NSAIDs derive from their ability to inhibit prostaglandin production through the inhibition of an important enzyme in the prostaglandin synthetic pathway, cyclo-oxygenase or COX. All NSAIDs have antipyretic, antalgic and anti-inflammatory properties, and are commonly used for the treatment of inflammatory diseases, especially musculoskeletal disorders, characterised by pain and inflammation. The most common adverse events of NSAIDs are gastrointestinal and cardiovascular effects (1).

1.2 Investigational Product

Ketoprofen lysine salt (KLS) is a propionic acid derivative and exerts an antipyretic action without interfering with the normal thermoregulatory processes. Painful inflammatory conditions are eliminated or attenuated facilitating articular mobility. The oral administration of the active ingredient in an aqueous solution leads to a rapid increase of plasma levels, an early attainment of peak values, a quicker onset and a higher intensity of the antalgic and anti-inflammatory effect. Ketoprofen binds to plasma proteins for 95-99%. The compound is extensively metabolised by the liver (about 60-80%) and elimination is essentially renal (1, 2).

1.3 Preclinical Data

Prolonged treatment in the rat, dog and monkey, with oral KLS at doses equivalent to or higher than the recommended therapeutic dose, did not cause any toxic events. KLS was found not to have mutagenic or carcinogenic effects in animals. The administration of inhibitors of prostaglandin synthesis has been shown to induce in animals an increase of pre and post-implantation losses, embryo-foetal lethality and various malformations, including cardiovascular (2).

1.4 Clinical Safety Data

In comparative studies, ketoprofen appears to be at least as effective as other anti-inflammatory and antalgic agents (3). The side effects of ketoprofen are similar to those of all NSAIDs, gastrointestinal disturbances being the most frequent: nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, more rarely peptic ulcerations, perforation, gastritis or gastrointestinal bleeding (3). Approximately 30% of patients experience mild gastrointestinal side effects with ketoprofen, which are decreased if the drug is taken with food or antacids (1). Other less frequent undesirable effects of ketoprofen are cutaneous events (urticaria, erythema, cutaneous rash), general events (allergic and anaphylactoid reactions), nervous events (dizziness and vertigo), cardiovascular events (palpitations, tachycardia, hypotension and hypertension) respiratory events (bronchospasm, dyspnoea), renal events (retention of water) and disorders of haematic crasis and of the urinary tract (2). In most of the cases, symptoms are temporary and resolve with the suspension of the therapy and with a specific pharmacological treatment (2).

OKiTASK® 40 mg as orodispersible granules was first approved for use in Italy on 17 September 2012 (International Birth Date).

The majority of the ADRs related to treatment with OKiTASK concerns events included in the SOC "Gastrointestinal Disorders", with upper abdominal pain as the most frequent reported term and the SOC "Nervous system disorders". The overall frequency of ADRs is very rare.
In the previous phase I clinical trials performed (KSL0109 - EudraCT 2009-015924-27 and KSL0112- CRO-PK-11-262, Swissmedic ref n° 2012DR1020) both OKi®, 80 mg soluble granules (half sachet – 40 mg) and OKiTASK® 40 mg orodispersible granules were well tolerated by healthy volunteers (4, 5).

1.5 Rationale

As a part of the Dompé extension line program, Dompé develops a new immediate release tablets formulation of ketoprofen lysine salt 40 mg.

The present bioequivalence phase I study is needed to compare the bioavailability and the concentration-time profile of the new immediate release formulation of KLS 40 mg with the reference compound OKi®, ketoprofen lysine salt 80 mg granules for oral solution (bipartite sachets).

The new immediate release tablets formulation of KLS 40 mg (corresponding to 25 mg of ketoprofen free acid) is expected to be essentially similar to the formulations of ketoprofen 25 mg for oral administration, that are already available in the European Community (e.g.: Toprec®, Rhone-Poulenc Rorer, France; Toprek®, Rhone-Poulenc Rorer, Italy, Fastum® 25 mg tablets, Menarini, Italy) with the same indications: pain such as episodic tension-type headache, dental pain, neuralgia, dysmenorrhoea, postpartum pain, muscular and osteoarticular pain.

1.6 Risks and benefits

Study subjects will not receive any direct therapeutic benefit from taking part in this study. No particular safety risks are foreseen with respect to the safety profile of the marketed OKi® 80 mg granules for oral solution. Considering that for test and reference the planned KLS dose is 40 mg and the IMP will be administered as a single dose with a wash-out period of 4 days, no concern for the safety of study participants is expected.

2 STUDY OBJECTIVES

The objective of the study is to investigate the bioequivalence between two formulations containing ketoprofen lysine salt (KLS) when administered as single oral dose in two consecutive study periods to healthy male and female volunteers under fasting conditions.

2.1 Primary end-point

- To evaluate the bioequivalent rate (C_{max}) and extent (AUC_{0-t}) of absorption of ketoprofen after single dose administration of test and reference.

2.2 Secondary end-points

- To describe the pharmacokinetic (PK) profile of ketoprofen after single dose administration of test and reference;
- to collect safety and tolerability data after single dose administration of test and reference.

3 CLINICAL SUPPLIES

3.1 Treatment

3.1.1 Description of products

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

3.1.1.1 Test product

TEST (T)

IMP	Ketoprofen lysine salt (KLS) immediate release tablets 40 mg, corresponding to 25 mg of ketoprofen free acid
Manufacturer (finished product)	Dompé s.p.a. – Via Campo di Pile snc – 67100 L'Aquila, Italy
Pharmaceutical form	Immediate release tablets
Dose	40 mg
Administration route	Oral

3.1.1.2 Reference product

REFERENCE (R)

IMP	OKi®: 80 mg granules for oral solution (bipartite sachets: each half sachet containing 40 mg of KLS corresponding to 25 mg of ketoprofen free acid)
Distributor	Dompé s.p.a. – Via Campo di Pile snc – 67100 L'Aquila, Italy
Manufacturer (finished product)	Dompé s.p.a. – Via Campo di Pile snc – 67100 L'Aquila, Italy
Pharmaceutical form	Granules for oral solution
Dose	40 mg (half of a bipartite sachet)
Administration route	Oral

3.1.2 Dose regimen

A single oral dose (40 mg) of each formulation (test and reference) will be administered to healthy volunteers under fasting conditions in two consecutive study periods with a wash-out interval of at least 4 days between the two administrations.

3.1.3 Route and method of administration

Test: One (1) tablet of test formulation will be administered to the subjects in the morning with 240 mL of still mineral water. Afterwards, no fluid intake will be permitted for 2 h.

Reference: the content of half sachet of the reference formulation will be dissolved in 190 mL of still mineral water. The entire solution will be drunk immediately by the subject. Then 50

mL of still mineral water will be used to rinse the glass and the rinse will also be drunk immediately. Afterwards, no fluid intake will be permitted for 2 h.

All subjects will be in fasting conditions from the evening before (at least 10 h, overnight).

The investigator will check that all subjects take the medication appropriately (mouth check).

3.1.4 Investigational product distribution

The test and reference IMP will be administered by the investigator or by his/her deputy. The IMP will be exclusively used for the present clinical study and will only be administered to the subjects enrolled in the study.

3.2 Packaging and labelling

The clinical centre will be provided with 30 subject individual boxes (subject kits). The number of kits is deemed sufficient for study stage 1 and 2. Each individual kit will contain 1 tablet of test and one bipartite sachet of reference formulation for the dosing of both periods.

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

a. Name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical study and emergency unblinding)
b. Pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open studies, the name/identifier and strength/potency
c. The batch and/or code number to identify the contents and packaging operation
d. A study reference code allowing identification of the study, site, investigator and sponsor if not given elsewhere
e. The study subject identification number/treatment number and where relevant, the visit number
f. The name of the investigator (if not included in (a) or (d))
g. Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)
h. “For clinical study use only” or similar wording
i. The storage conditions
j. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity
k. “Keep out of reach of children”

Labels will be in English.

The sponsor will provide a reserve kit for each subject to be used if needed.

3.3 Storage conditions

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

3.4 Drug accountability

The test and reference IMPs will be provided directly to the investigator by the sponsor, in excess of the amount necessary for the study.

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

At the end of the study, used, unused and partially used supplies of test and reference IMPs provided by the sponsor will either be destroyed on site (upon written authorisation) or returned to the sponsor, after assessment of drug accountability.
In the event that the IMPs will be destroyed on site, a destruction certificate will be provided to the sponsor

4 INVESTIGATIONAL PLAN

4.1 Overall study design

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

4.2 Discussion of design

The trial has been designed in agreement with the "Guideline on the investigation of bioequivalence" (CPMP/QWP/EWP/1401/98 Rev. 1, 20 January 2010) (9, 10).

Due to the lack of information about the PK profile of the new formulation it was not possible to calculate the sample size properly.
For this reason it was decided to use a "two stage" bioequivalence study design. The sample size of 30 subjects is regarded as sufficient to satisfy the primary objective for the first stage of the study.
After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should bioequivalence be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power of at least 80%, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage or should it be proven with an *a posteriori* calculated power lower than 80%, the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. The Sponsor will decide whether the study has to continue or not. In the first case, the additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages. The second stage will be performed after notification of the sample size to the local Ethics Committee and to the central Swiss authority (Swissmedic).

An open design was chosen as it was considered adequate to evaluate objective measures such as pharmacokinetic parameters. All the personnel involved in the analytical determinations of the ketoprofen in the plasma samples withdrawn from the volunteers will be maintained in blinding.

The sequence of treatments in the two study periods will be assigned to each randomised subject according to a computer generated randomisation list (see § 8.1).

A wash-out period of at least 4 days between the two administrations is justified by the elimination half-life of the ketoprofen (1-2 h).

5 STUDY POPULATION

5.1 Target population

The study population will include 30 healthy volunteers (at least 12 subjects per sex) aged 18-55 years inclusive in the first study stage

5.2 Inclusion criteria

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

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: males/females, 18-55 years old inclusive
3. *Body Mass Index (BMI)*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure (SBP) 100-139 mmHg, diastolic blood pressure (DBP) 50-89 mmHg, pulse rate (PR) 50-90 bpm and body temperature (BT) ≤ 37.5° C, measured after 5 min of 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 (females only)*: females of child-bearing potential and with an active sexual life 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 [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
   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 female subjects, pregnancy test result must be negative at screening.

5.3 Exclusion criteria

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

1. *Electrocardiogram (ECG 12-leads, supine position)*: clinically significant abnormalities
2. *Physical findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values indicative of physical illness

4. *Allergy*: ascertained or presumptive hypersensitivity to the active principles (ketoprofen) and/or formulations' ingredients; history of hypersensitivity to drugs (in particular to NSAIDs) or allergic reactions in general, which the Investigator considers may affect the outcome of the study
5. *Diseases*: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory (including asthma), skin, haematological, endocrine or neurological and autoimmune diseases that may interfere with the aim of the study
6. *Medications*: medications, including over the counter (OTC) drugs [in particular ketoprofen and acetylsalicylic acid (ASA) and NSAIDs in general], herbal remedies and food supplements taken 2 weeks before the start of the study. Hormonal contraceptives for females will be allowed
7. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study (date of the informed consent signature)
8. *Blood donation*: blood donations for 3 months before this study
9. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [> 1 drink/day for females and > 2 drinks/day for males, defined according to the USDA Dietary Guidelines 2010 (6)], caffeine (> 5 cups coffee/tea/day) or tobacco abuse (≥ 6 cigarettes/day)
10. *Drug test*: positive result at the drug test at screening
11. *Alcohol test*: positive alcohol breath test at day -1
12. *Diet*: abnormal diets (< 1600 or > 3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
13. *Pregnancy (females only)*: positive or missing pregnancy test at screening or day -1, pregnant or lactating women

5.3.1 Not allowed treatments

No medication, including OTC [NSAIDs in particular ketoprofen and acetylsalicylic acid (ASA)] and herbal remedies and food supplements, will be allowed for 2 weeks before the start of the study and during the whole study duration.

5.3.2 Allowed treatments

Paracetamol will be allowed as therapeutic counter-measure for adverse events (AEs) according to the investigator's opinion. Hormonal contraceptives will be allowed too.
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.

6 STUDY SCHEDULE

The schedule of the study is summarised at page 10.

6.1 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 4 days. Minimum study duration will be 7 days, screening visit included. Maximum study duration will depends to the wash out period followed. 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 -14 and day -2
  - Period 1 – visit 2: day -1

- **Interventional phase**
  - Period 1 – visit 3: day 1
  - Wash-out interval of at least 4 days
  - 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)

Visit	Day	Procedures/Assessments	Notes
Screening – visit 1	*From day -14 to day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number (as S001, S002, etc.) ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, vital signs, physical abnormalities) ➢ ECG recording ➢ Laboratory analyses: haematology, blood chemistry, urine analysis, serum virology and serum pregnancy test (females only) ➢ Urine multi-drug kit test ➢ AE monitoring ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the clinical centre source document only and will not be transferred to the sponsor
Visit 2	*Day -1*	➢ Alcohol breath test ➢ Vital signs measurement ➢ Urine pregnancy test (females only) ➢ AE and concomitant medications ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and Randomisation	Arrival at the clinical centre in the evening Confinement until the evening of day 1 Standardised low-fat dinner Fasting for at least 10 h (overnight)
Visit 3	*Day 1*	➢ IMP administration: 8:00 ± 1h ➢ Vital signs measurement: 8h post-dose ➢ Blood sample collection for PK analysis: pre-dose (0), 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6 and 8 h post-dose ➢ AE and concomitant medications	<u>Day 1</u> Standardised lunch at 13:00 (5 h post-dose) Discharge from the clinical centre in the evening after the 8 h blood sample collection and vital signs check
Wash-out	*At least 4 days*	A wash-out interval of at least 4 days between the two administrations of the two study periods	
Visit 4	*Day -1*	As visit 2, with the exclusion of Inclusion/exclusion criteria evaluation, Eligibility evaluation, Enrolment and Randomisation	Arrival at the clinical centre in the evening Confinement until the evening of day 1 Standardised low-fat dinner Fasting for at least 10 h (overnight)

Visit	Day	Procedures/Assessments	Notes
Visit 5	*Day 1*	As visit 3. Test or reference IMP administered according to the randomisation list and cross-over design	Day 1 Standardised lunch at 13:00 (5 h post-dose) Final discharge from the clinical centre after the 8 h blood sample collection and final visit
Final Visit/ETV	*Day 1 of period 2 / at ETV in case of discontinuation*	➢ Full physical examination (body weight , physical abnormalities and, in case of ETV, vital signs) ➢ ECG recording ➢ Laboratory analyses as at screening, with the exception of virology, urine drug test and pregnancy test ➢ AE and concomitant medications In case of clinically significant results at the final visit, the subjects will be followed-up by the investigator until the normalisation of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the investigator in case of occurrence of any adverse reactions

6.2 Diet and lifestyle

During confinement, the subjects will not take any food or drinks (except water) for at least 10 h (i.e. overnight) before IMP administration. Water will be allowed as desired, except for one h before and two h after IMP administration. In order to maintain an adequate hydration, the subjects will be encouraged to drink at least 180 mL of mineral water every 2 h for 6 h post-dose, starting at 2 h post-dose.
In the evening of day -1, the subjects will receive a standardised light and low-fat dinner.
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.

Coffee, tea and any other food containing xanthines (i.e. coke, chocolate, etc.) will be forbidden during confinement. Alcohol and grapefruit will be forbidden from 48 h before the first administration until the end of the study.
During confinement, routine ambulant daily activities will be strongly recommended.

The subjects will be allowed to smoke not more than 1 cigarette after lunch.

6.2.1 Restrictions

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

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

7 DESCRIPTION OF SPECIFIC PROCEDURES

7.1 Physical examination

A full physical examination will be performed at the screening and final visits.
Information about the physical examination will be recorded by the Investigator. Any abnormality will be recorded. Significant findings/illnesses, reported after the start of the study and which meet the definition of an AE (see § 11), will be recorded.

7.1.1 Body weight and height

Body weight will be recorded at:

- Screening and final/ETV visit

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]).

7.1.2 Vital signs

Blood pressure (BP), pulse rate (PR) and body temperature (BT) will be measured by the Investigator or his/her deputy after 5 min of rest (sitting position).

Measurements will be performed at:

- Screening visit;
- On day -1 of each period;
- 8 h post-dose of each period (on day 1, visit 5, the measure will correspond to the values of the final visit);
- at early termination visit (if applicable).

Body temperature will be measured in the ears.

7.1.3 ECGs

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

7.2 Clinical laboratory assays

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

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

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

Serum pregnancy test (women).
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 clinical centre.

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

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

DRUG SCREENING
A urine drug test will be performed at the clinical centre at screening, using a urine multi-drug kit. The following drugs will be assessed: cocaine, amphetamine, methamphetamine, cannabinoids (delta-9-tetrahydrocannabinol - THC), opiates and ecstasy.
The same analyses, with the exception of urine drug test, virology and serum pregnancy test, will be performed at the final visit/ETV.

7.3 Sampling for pharmacokinetic analysis

7.3.1 Venous blood sampling

Venous blood samples (8 mL) will be collected from a forearm vein at the following times:

- pre-dose (0), 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6 and 8 h post-dose

Actual sampling times for each subject will be recorded in the individual case report forms (CRFs). Deviations in actual sampling times should not exceed the recommended ranges reported in the following table. Any deviations outside the recommended ranges will be verified through Data Clarification Forms and will not automatically lead to the exclusion of the concerned subjects from the PK Sets.

Table 7.3.1.1 Recommended maximal deviations from the scheduled sampling times

Sampling time	Deviation
Pre-dose (0)	Within 30 minutes before IMP administration
0.0833 h (5 min), 0.25 h (15 min)	0 min
0.5 h (30 min)	± 1 min
0.75 h (45 min)	± 2 min
1, 1.5 h	± 3 min
2, 3, 4 h	± 5 min
5, 6, 8 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 6 mL will be collected from the catheter and transferred with a syringe into heparinised tubes (Li-heparin).

The samples will be stored on ice for a maximum of 15 min. Then the samples will be centrifuged at 4° C for 10 min at 2500 g to obtain plasma. Each plasma sample will be immediately divided into two aliquots, P1 and P2, in pre-labelled polypropylene tubes, and stored frozen at ≤-20° C until analyses.

If any clinical assessment, such as vital signs measurement or ECG recording, is foreseen at the same time-point of blood sampling for PK analysis, blood collection will be performed at the scheduled time. However, vital signs and ECG parameters can be influenced by the blood sampling. Therefore, these assessments can be performed up to 30 min before the collection of the pre-dose PK sample and up to 10 min before the collection of the other scheduled PK samples. Any deviations outside the recommended time will be verified through Data Clarification Forms. However, since vital signs measurements and ECG recordings will be performed for safety reasons only, deviations from the planned time schedule will be considered not relevant.

7.3.2 Analytics

The concentration of ketoprofen will be determined in plasma at Dompé Bioanalytical Laboratories in L'Aquila, Italy using a fully validated HPLC-UV (High Performance Liquid Chromatography) assay.

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

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

7.3.3 Labelling, storage and transport of samples

7.3.3.1 Samples labelling

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

Study code	Study code CRO-PK-14-288 - Sponsor code KLS0114
Subject number	001-030 (first stage)
Tube identification	P1/P2
Period	1, 2
Scheduled sampling time	as h; see § 7.3.1

7.3.3.2 Samples storage and transport

During the study the samples will be stored at ≤- 20° C. At the end of each collection day, aliquots 1 and 2 will be stored in separate freezers.

All aliquots 1, packed in sufficient solid CO_2, will be shipped by an authorised courier from Cross Research Phase I Unit to Dompé Bioanalytical Laboratories in L'Aquila, Italy. Aliquots 1 will remain stored at Dompé Bioanalytical Laboratories until the finalisation of the bioanalytical report. Afterwards, the samples will be destroyed and a certificate of destruction will be provided to the sponsor.

The counter-samples (aliquot 2) 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 aliquots 1, 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

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.

7.4 Total number of samples and blood withdrawn

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

For routine laboratories analysis:
Screening visit: 12.5 mL
Final visit/ETV: 12.5 mL

For *PK* analysis:
Treatment T: 8x13=104 mL
Treatment R: 8x13=104 mL

In total 233 mL of blood (not exceeding a normal blood donation) will be withdrawn from each subject.

8 ASSIGNMENT OF STUDY TREATMENT

8.1 Randomisation

The randomisation list will be computer-generated by the Biometry Unit of the Clinical Contract Research Organization (CRO), using the PLAN procedure of the SAS® version 9.3 (TS1M1) (8) or higher (the actual version will be stated in the final report). The randomisation list will be supplied to the study site before study start. The randomisation list will be attached to the final clinical study report.

8.2 Treatment allocation

Subjects will be assigned to the sequence of treatments (TR or RT) in the two study periods according to the randomisation list. Subjects will be randomised to receive one of the two treatments (i.e. either test or reference) during period 1 and the other treatment during period 2.
Randomisation number will be given to the subjects on study day -1, period 1, and will be used to assign the treatment sequence according to the randomisation list, as detailed above.

8.3 Blinding

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

9 EVALUATION PARAMETERS

9.1 Study variables

9.1.1 Primary variables

- C_{max} and AUC_{0-t} of ketoprofen calculated from plasma concentrations after single oral dose of test and reference.

9.1.2 Secondary variables

- $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, λ_z and F_{rel} of ketoprofen calculated from plasma concentration after single oral dose of test and reference;
- Treatment-emergent AEs (TEAEs), vital signs (BP, PR, BT), body weight, ECG, laboratory parameters.

9.2 Pharmacokinetic assessments

9.2.1 Pharmacokinetic parameters

The following PK parameters will be measured and/or calculated for ketoprofen, using the validated software Phoenix WinNonlin® version 6.3 (7) or higher (actual version will be stated in the final report):

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

AUC_{0-t} is considered a reliable estimate of the extent of absorption if the ratio $AUC_{0-t}/AUC_{0-\infty}$ equals or exceeds a factor of 0.8, i.e. if $\%AUC_{extra}$ is <20%.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a correlation coefficient $R^2 > 0.8$.

9.3 Safety assessments

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

10 STATISTICAL METHODS

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

Not available data will be evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (8) or higher (the actual versions will be stated in the final report).
The statistical analysis of PK parameters will be performed using Phoenix WinNonlin® version 6.3 (7) or higher and SAS® version 9.3 (TS1M1) or higher.

10.1 Analysis Sets

10.1.1 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/she will be defined as a screen failure.

A subject will be defined as enrolled in the study if he/she is included into the interventional phase of the study. The enrolment can be performed through randomised or non-randomised allocation to a treatment arm/treatments sequence.

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

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

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

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.

10.1.2 Reasons for exclusion from the PK set

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

Before bioanalysis

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

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

After bioanalysis

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

- subjects with lack of any measurable concentrations or only very low plasma concentrations for the reference medicinal product. A subject is considered to have very low plasma concentrations if his/her AUC is less than 5% of the reference medicinal 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 the reference medicinal product. The exclusion of these subjects must be justified on the basis of sound scientific reasons and mutually agreed between the CRO and the Sponsor
- subjects with non-zero baseline concentrations > 5% of C_{max}

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

10.2 Sample size and power considerations

In a first study stage 30 healthy volunteers (at least 12 subjects per sex) will be included and treated to receive both test and reference investigational product according to the cross-over design. Drop-out subjects will not be replaced. After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should bioequivalence be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power of at least 80%, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage or should it be proven with an *a posteriori*

calculated power lower than 80%, the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. The Sponsor will decide whether the study has to continue or not. In the first case, the additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages.

10.3 Interim analysis at the end of study stage 1

An interim bioequivalence test on the available PK data will be performed at the end of stage 1, as described in § 4.2 above. Should bioequivalence not be proven at this stage, the sample size for the study (study stage 1 and 2) will be calculated on the basis of the interim bioequivalence test results.

The second stage will be performed after notification of the sample size to the local Ethics Committee and to the central Swiss authority (Swissmedic).

10.4 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.

10.5 Analysis of pharmacokinetic parameters

10.5.1 Descriptive pharmacokinetics

A descriptive PK will be presented. The results will be displayed and summarised in tables and figures. Individual and mean curves (+SD at sampling times), indicating inter-subject variability, will be plotted. 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). The date and time of PK sample collection will be listed by treatment.

10.5.2 Statistical comparison of pharmacokinetic parameters

According to the current European Guideline on the Investigation of Bioequivalence (9) and the European Questions & Answers document (10), the PK parameters AUC_{0-t}, $AUC_{0-\infty}$ (if feasible) and C_{max} will be analysed using ANOVA. Before analysis, the data will be transformed using a neperian logarithmic transformation. ANOVA will be performed on the data from study stage 1 taking into account treatment, period, sequence and subject (sequence) as sources of variation. For the analysis of the combined data of stage 1 and stage 2 (if any), stage, treatment, period (stage), sequence, sequence*stage and subject (sequence*stage) will be taken into account as sources of variation.

For both the interim analysis (stage 1 data) and the final combined analysis (stage 1 and 2 data, if any), acceptance criterion for bioequivalence will be a 94.12% confidence interval for the T/R ratio of the geometric means of the PK parameters under consideration within the

80.00-125.00% range, according to the current guidelines for bioequivalence studies and to the Pocock α spending function.

t_{max} will be compared between treatments using the non-parametric Friedman test.

10.6 Safety and tolerability evaluation

- **AEs**

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 and not worsening after the first dose of IMP
- TEAEs: all AEs occurring or worsening after the first dose of IMP

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

- **Physical examination**

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see § 11), will be recorded in the subject source documents. Date of the physical examination and overall investigator's interpretation (as normal [N], abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF.

- **Laboratory data**

Date/time of samples collection and overall investigator's interpretation (N, NCS or CS) will be recorded in the CRF and listed in the final clinical study report. Hard copies of the laboratory print-outs will be attached to the CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. All laboratory results will be listed and a table of all the abnormal values will be presented.

- **Vital signs**

Values of vital signs will be listed and summarised by descriptive statistics.

- **Body weight**

Values of body weight will be listed and summarised by descriptive statistics.

- **ECG**

Date/time of ECG recording and overall investigator's interpretation (N, NCS or CS) will be reported in the CRF and listed in the final clinical study report. Hard copies of the ECGs will be attached to the CRF. All clinically significant abnormalities after the screening visit will be recorded as AEs.

11 DEFINITION AND HANDLING OF ADVERSE EVENTS (AEs)

11.1 Applicable SOPs

AE definition, classification and management will follow the Sponsor SOPs, based upon applicable local and international regulations. An operative summary of relevant SOPs will be made available to the clinical centre, as appropriate. The monitoring of AE will start from the Informed Consent signature.

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

11.2 Definitions

11.2.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, which does not necessarily have a causal relationship with the study treatment (Directive 2001/20/EC). An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

11.2.2 Non-Serious Adverse Event (SAE) Definition

A non-serious AE is defined as any untoward change in a subject's medical conditions that does not meet serious criteria noted below (e.g., is not fatal, is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.).

11.2.3 Serious Adverse Event (SAE) Definition

A serious adverse event (SAE) is defined in line with Directive 2001/20/EC as any adverse experience that meets any of the following criteria:

- results in death
- is life-threatening

  (NOTE: Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe)

- requires inpatient hospitalization or prolongation of existing hospitalization

  (NOTE: In general, hospitalization means that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When

in doubt as to whether "hospitalization" occurred, the event should be considered serious

- results in persistent or significant disability/incapacity

  (NOTE: 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, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a *substantial disruption)*

- results in a congenital anomaly/birth defect
- is an important medical event

  (NOTE: An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject's well being and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization or the development of drug dependency or drug abuse)

11.2.4 Reference Safety Information (RSI)

In order to assess whether an adverse reaction is expected, the Investigator's Brochure (IB) for test formulations and the leaflet for the reference formulations will be used.

11.3 Unexpected Adverse Reaction

An unexpected adverse reaction is an adverse reaction, the nature and severity of which is not consistent with the information in the Investigator's Brochure relating to the study or in the case of a product with a marketing authorisation, the summary of product characteristics. The Sponsor will be responsible for ensuring that the Investigator is provided with an up to date Investigator's Brochure for the test investigational product and the SmPC for the reference compound (see attachment 1 of the Investigator's Brochure).

11.4 Documentation

All data related to an AE, type of event, onset date, intensity (mild, moderate or severe), relationship with study drug or other relevant information, must be reported in the specific section of CRF, including abnormal laboratory values.

11.5 Assessment of Adverse Event Severity and Relationship

For every AE, the Investigator must assess the intensity (severity) and causality (relationship to study treatment). Specifically, the intensity of events should be classified as mild,

moderate, or severe. The assessment of causality will be based upon the categories of related and not related. These classifications should be based on the following definitions:

Table 11.5.1 Intensity (Severity) of the Adverse Event

Mild	**Grade 1 -** Does not interfere with subject's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	**Grade 2** - Interferes to some extent with subject's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	**Grade 3 -** Interferes significantly with subject's usual function (incapacity to work or to do usual activities [unacceptable])

Table 11.5.2 Relationship of the Adverse Event to the Investigational Product

None (Intercurrent Event)	An event that is not and cannot be related to the investigational product, e.g. subject is a passenger in a road traffic accident
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations
Possible	Relationship may exist, but could have been produced by the subject's condition or treatment or other cause
Probable	Relationship is likely, the AE abates upon discontinuation of investigational product and cannot be due to the subject's condition
Highly Probable	Strong relationship, the event abates upon discontinuation of investigational product and, if applicable, re-appears upon repeat exposure

11.6 Type and Duration of the Follow-up of Subjects after Adverse Events

AE will be followed by the Investigator (by phone or visit) until resolved or considered stable. Outcome of AEs will be defined as:

- ***Resolved***. Subject recovered from AE/SAE without any after‐effect of disease or injury.
- ***Resolving***. Subject is not completely recovered from AE/SAE at the time of reporting, but conditions improved.
- ***Not Recovered***. Subject has not recovered or AE/SAE is currently ongoing at the time AE/SAE Form is completed.
- ***Recovered with Sequelae***. Subject recovered from AE/SAE but after‐effect of disease or injury resulted. Please specify what sequelae resulted in Section "Narrative".
- ***Fatal***. SAE directly resulted in death of the Subject. If death is checked, complete the appropriate section "Details of Death".
- ***Unknown***. Outcome is unknown. Check box when no information is available at the time the SAE Form is completed. Follow up information on the outcome should be provided.

11.7 Reporting

Adverse Events:
All AEs (non-serious and serious) which occur during the course of the study will be recorded in the CRF. Any pre-existing medical conditions or signs/symptoms present in a subject prior to the start of the study (i.e., before informed consent is signed) should be specified in the CRF. Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on the CRF. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (i.e., severity), any action with study treatment taken as a result of the event, and an assessment of the adverse event relationship to the study treatment.
Serious Adverse Events:
The Investigator must record all SAEs, occurring at any time during the study regardless of presumed causal relationship, on the Serious Adverse Event form. Within 24 hours from first knowledge of the SAE, the Investigator shall send the filled in and signed SAE form to the CRO and to the Sponsor at the following addresses:

Sponsor
Dompé Drug Safety
Laura Boga, Senior Safety Manager
Email to: farmacovigilanza@dompe.it
or Fax: +39.02.36026913

Dompé Medical Expert
Elisabetta Grillo,
Email to: elisabetta.grillo@dompe.it
or Fax: +39.02.58383297

Dompé Clinical Development Manager
Mauro Ferrari
Email to: mauro.ferrari@dompe.it
or Fax: +39.02.58383324

CRO:
Email to: angelo.vaccani@croalliance.com
or Fax to: +41.91.630.05.11

If assistance is needed with the reporting of a SAE, contact details for the CRO/Sponsor are provided in the section “Study Responsible Person”(§ 16).
Serious adverse events will be managed directly by the Dompé Drug Safety department, with CRO support for Follow Up requests.

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

Depending on the nature and seriousness of the AE, the Sponsor may request further information, including copies of appropriate medical records of the subject, as well as results of laboratory tests performed. If the subject was hospitalized, a copy of the discharge summary should be provided to the Sponsor as soon as it is available, if possible.
In any case, the Investigator shall further follow up each SAE to complete case information till resolution of the event, as appropriate, and provide the follow up information to the Sponsor .Follow-up SAE information should be communicated through a new SAE form duly filled in and signed, within 24 hours from awareness, to:
Dompé Drug Safety (e-mail: farmacovigilanza@dompe.it or Fax: +39 02 36026913), Dompé Medical Expert (elisabetta.grillo@dompe.it), Dompé Clinical Development Manager (mauro.ferrari@dompe.it) and CRO (angelo.vaccani@croalliance.com) whenever becoming aware of new available information regarding the SAE, once the condition is resolved or stabilized and when no more information about the event is expected.

Any additional data from these follow-up procedures must be documented and made available to the Sponsor who will determine when the data need to be documented in the CRFs.

11.8 Reporting Procedure to IEC and to Regulatory Authorities

The Sponsor, within 2 working days from the receipt of a serious adverse event including fatal or life threatening events, shall perform an assessment of the expectedness and the causality of each serious adverse event.
Expectedness will be assessed with respect to the current Investigator's Brochure for the test formulation and leaflet for the reference formulation.
For a serious adverse event reported by the Investigator as not related that is subsequently revised to be related by the Sponsor, the Investigator will receive a notification.
Events considered "Possible", "Probable" and "Highly Probable" related to the IMP treatment will be reported to appropriate regulatory authorities.

During the course of the clinical trial, Dompé shall report any suspected unexpected serious adverse reaction (SUSAR) case to the Competent Authority (according to specific law requirements) while the CRO shall submit SUSAR case to the concerned IEC which approved the protocol as soon as possible and in no event later than:

(*a*) seven calendar days after becoming aware of the information if the event is fatal or life threatening;
(b) fifteen calendar days after becoming aware of the information if the event is neither fatal nor life threatening.

Dompé shall, within eight days after having informed the IEC/Competent Authority under paragraph (a), submit a complete report in respect of that information that includes an assessment of the importance and implication of any findings, made on the basis of follow up information provided by the Investigator.

The Sponsor shall be responsible to prepare and submit periodical update reports as appropriate.

11.9 Follow-up of Subjects with Adverse events

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. All AEs should be followed-up to determine outcome of the reaction or until 10 days after the final visit. The Investigator should follow-up the event until resolution or stabilization of the condition. It is the Investigator's responsibility to assure that the subjects experiencing AEs receive definite treatment for any AE, if required.

11.10 Pregnancy in the Clinical Trial

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Adequate birth control methods are summarized in the protocol's exclusion criteria.

Prior to enrolment in the clinical trial, female subjects of childbearing potential and their partners must be advised of the importance of avoiding pregnancy during the entire course of the study treatment and for the 30 days after the study treatment period ends and of the potential risks associated with an unintentional pregnancy. During the trial, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant; in the same way, male subjects who become aware that the partner might be pregnant, are to be instructed to contact the Investigator immediately. The study Sponsor must be contacted immediately and a decision will be made regarding continuation of the pregnant woman in the study based upon the circumstances surrounding the pregnancy. Pregnancy is not reportable as an adverse event; however, complications may be reportable and will be assessed for reportability on a case by case basis. A form prepared by the Sponsor will be utilized to capture all pregnancy-related information until the birth of the child for both the subject and the partner during the study treatment period (4 weeks) and follow-up period (total 8 weeks).

12 DATA MANAGEMENT PROCEDURES

12.1 Data collection – CRFs

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

12.2 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. KSL0114), 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 ("/") [example: KSL0114/001/S001/001]. The last 8 digits of the unique subject identifier (enrolled subjects), corresponding to the subject screening and subject randomisation numbers separated by a slash, or the last 4 digits of the unique subject identifier (not enrolled subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the clinical study report and will be used to identify the subjects in in-text tables or wording (if applicable) [example: S001/001].

12.3 Database management

The CRO will provide double data entry with 100% sight verification of data by a second data entrist and discrepancy resolution by a third individual and will update and verify the database and create the final SAS data sets. The final data file will be transferred to the sponsor in the agreed format with all the other study documentation.

12.3.1 Coding dictionaries

Medical/surgical history and underlying diseases, 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.

13 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The monitoring visits will be conducted by appropriate staff of Clinical Medical Service Sagl, Switzerland.

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.

13.2 Quality Control and Quality Assurance

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

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

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

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

13.3 Applicable SOPs

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

13.4 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.

13.5 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.

14 ETHICAL CONSIDERATIONS

14.1 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 general principles of "ICH Topic E6, CPMP/ICH/135/95", July 1996 including post Step 4 errata, status September 1997 and post Step errata (linguistic corrections), July 2002.

14.2 Informed consent

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

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

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

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

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements (see § 15.3). 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 form, that informed consent has been obtained.

14.3 Insurance policy

The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

14.4 Withdrawal of subjects

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

14.4.1 Primary reason for discontinuation

- **Adverse event**: any (significant) adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 11.2.
- **death**: the absence of life or state of being dead
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**: pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

14.4.2 Discontinuation procedures

For any subject discontinuing the study, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening)
- arrange for alternative medical care of the withdrawn subject, if necessary

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

Discontinued subjects will not be replaced.

14.5 Study termination

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

15 ADMINISTRATIVE PROCEDURES

15.1 Material supplied to the clinical centre

Beside IMP(s), 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 investigator's brochure (IB) relative to the IMP
- informed consent forms

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

15.2 Protocol amendments

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

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

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

15.3 Study documentation and record keeping

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

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

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

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as

required by the applicable regulatory requirement(s). The period of documents retention by CRO and Sponsor will be according to ICH-GCP chapter 5.5.11.
According to the national regulations the clinical site will retain the study documentation for at least 10 years from the end of the study. The study documents destruction will be performed after sponsor authorisation.

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.

15.4 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.

15.5 Confidentiality and data protection

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

Data on subjects collected in the CRFs during the study will be documented in an anonymous way (see § 12.2). 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.

15.6 Publication policy

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

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

16 STUDY RESPONSIBLE PERSONS

16.1 Sponsor

Dompé s.p.a. - Via Campo di Pile; I-67100 L'Aquila, Italy
Milan Offices: Via S. Santa Lucia 6, I-20122 Milan, Italy
Phone: +39.02.583831
Fax: +39.02.58383324

Sponsor representative

Clinical Development Manager
Mauro P. Ferrari, PharmD
Email: mauro.ferrari@dompe.it

Research & Development Director
Marcello Allegretti, ChemD
Email: marcello.allegretti@dompe.it

Medical Expert
Elisabetta Grillo, MD
Email: elisabetta.grillo@dompe.it

Dompé Drug Safety
Laura Boga, BscD
Email: farmacovigilanza@dompe.it

16.2 Institutes performing the study

16.2.1 Clinical centre

CROSS Research S.A. – Phase I Unit, Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41.91.63.00.510
Fax: +41.91.63.00.511
Email: clinic@croalliance.com

Principal investigator
Milko Radicioni, MD

Co-investigator
Antonio Rusca, MD, FMH

16.3 Drug assay

Dompé Analytical Laboratories S.p.A. - Via Campo di Pile; I-67100 L'Aquila, Italy
Phone: +39.0862.338367
Fax: +39.0862.338219
Mobile: +39 347 4838904

Email: danniballe@dompe.it

Analytics representative
Gaetano D'Anniballe, BSc

16.4 Centralised clinical laboratory

Unilabs Ticino, via Rovere 8, CH-6932 Breganzona, Switzerland
Phone: +41.91.960.73.73
Fax: +41.91.960.73.74
Email: bmathis@unilabs.ch

16.5 Co-ordination, data analysis & reporting

CROSS S.A., Switzerland, and its affiliated companies CROSS Research S.A. and CROSS Metrics S.A., sharing the same quality assurance system.

CROSS Research S.A.
Via F.A. Giorgioli 14, CH-6864 Arzo, Switzerland

Coordination
Angelo Vaccani, PhD, Clinical Project Leader
Email: angelo.vaccani@croalliance.com

Pharmacokinetic Analysis
Luca Loprete, MSc, Senior Pharmacokineticist
Email: luca.loprete@croalliance.com

Biometry Unit Representative
Matteo Rossini, Biometry Manager, MSc, Unit Head
Email: statistics@croalliance.com

Quality Assurance Unit Representative
Maurizio Cuocolo, PharmD, Quality Assurance
Email: qau@croalliance.com

16.6 Monitoring

Clinical Medical Service Sagl
Via Collina Azzurra 8, CH-6900 Paradiso, Switzerland
Legal address: Via Motta 24, CH-6830 Chiasso, Switzerland
Mobile: +41.79.827.27.67
Fax: +41.91.649.57.14
Email: cmed@cmed.ch

17 REFERENCES

1. Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 11th Edition, 2006.
2. OKi®. Summary of Product Characteristics.
3. Veys EM. 20 years' experience with ketoprofen. Scand J Rheumatol Suppl. 1991;90:Suppl 1-44.
4. Three way crossover, randomised, single dose comparative bioavailability phase I study of ketoprofen lysine salt as orodispersible granules (40 mg administered with or without water) versus ketoprofen lysine salt as granules for oral solution (80 mg bipartite sachet, half sachet) after oral administration to healthy volunteers of both sexes. Dompé S.p.A., 2009, report on file.
5. Two-way crossover, randomised, single dose bioequivalence phase I study of ketoprofen lysine salt as orodispersible granules (40 mg administered without water) versus ketoprofen lysine salt as granules for oral solution (80 mg bipartite sachet, half sachet) after oral administration to healthy volunteers of both sexes. . Dompé S.p.A., 2012, report on file.
6. U.S. Department of Health and Human Services and U.S. Department of Agriculture, Nutrition and your health: Dietary Guidelines for Americans, 2010
7. Phoenix 1.3 User's Guide, Pharsight Corporation
8. SAS/STAT® User's Guide
9. Guidance on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/Corr **, 20 January 2010
10. Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party. EMA/618604/2008 Rev. 8, 10 October 2013

AMENDMENT Nr. 1

EC ref. n°: CE 2840; Swissmedic ref. n°: 2014DR1181

Study CRO-PK-14-288 - Sponsor code KSL0114

TITLE:

Two-way crossover, randomised, single dose and two-stage bioequivalence phase I study of ketoprofen lysine salt as immediate release tablets formulation (40 mg) versus ketoprofen lysine salt as granules for oral solution (80 mg bipartite sachet, half sachet) after oral administration to healthy volunteers of both sexes

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

***REASON*:**

The present amendment introduces the following changes in the study protocol:

- The assumptions regarding the expected point estimate for the T/R ratio of the geometric means, the expected variability, the type I error level and the power used for the estimation of the number of subjects included into the stage 1 are clearly stated in the relevant sections of the study protocol
- On the basis of the *a priori* power analysis for the calculation of the stage 1, the *a posteriori* power analysis in case the bioequivalence will be proved with the results of the subjects of the first stage, is no more necessary and has been removed
- The stopping criteria of the study have been amended in order to avoid uncontrolled inflation of type I error due to the enrolment of a too high number of subjects in the stage 2 (overpowered bioequivalence)

The following scientific publications justify the changes decided for the statistical section.

1. Fuglsang A. Futility rules in bioequivalence trials with sequential designs. AAPS Journal 2013, 16: 79-82
2. Montague TH, Potvin D., DiLiberti CE., et al. Additional results for sequential design approaches for bioequivalence studies with crossover design. Pharmaceut. Statist. 2012, 11:8-13
3. Potvin D., DiLiberti CE., Hauck WW., et al. sequential approaches for bioequivalence studies with crossover designs. Pharm Stat. 2008 Oct-Dec;7(4):245-62

The present amendment also introduces the following minor changes in the study protocol:

- Federico Saibene, MD, replace Elisabetta Grillo, MD, as medical expert of the study

- The name of the company in charge of the study monitoring changed. Clinical Medical Service Sagl is now Clinical Medical Services di Maria Pia Savorelli
- Chiara Leuratti has been added as Medical Writing Department representative for reporting activities
- Dompè s.p.a will be replaced by Dompè farmaceutici s.p.a. with effective date from 01 December 2014. The change resulted from a merge of the two companies. No impact on the study is foreseen. A simplified procedure was followed since Dompè s.p.a was 100 % owned by Dompè farmaceutici s.p.a.. As result of this change the insurance has been updated.

This amendment is considered substantial because the changes in the statistical section will affect the stopping criteria of the study and the evaluation of the primary objective, whereas the subject safety and the number of the subjects foreseen in the stage 1 are not affected.

Changes from study protocol Final version 1.0, 28JUL2014 are outlined below.
The amended text is in bold characters; the deleted text is in bold characters and crossed-out with a deleting line (deleted text still visible).

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 4.2 "Discussion of design" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

…

Due to the lack of information about the PK profile of the new formulation it was not possible to calculate the sample size properly.
For this reason it was decided to use a "two stage" bioequivalence study design. The sample size of 30 subjects is regarded as sufficient to satisfy the primary objective for the first stage of the study.
After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should bioequivalence be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power of at least 80%, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage or should it be proven with an *a posteriori* calculated power lower than 80%, the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. The Sponsor will decide whether the study has to continue or not. In the first case, the additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages. The second stage will be performed after notification of the sample size to the local Ethics Committee and to the central Swiss authority (Swissmedic).

…

AMENDED TEXT:

…

Due to the lack of information about the PK profile of the new formulation it was not possible to calculate the sample size properly.
~~**For this reason it was decided to use a "two stage" bioequivalence study design. The sample size of 30 subjects is regarded as sufficient to satisfy the primary objective for the first stage of the study.**~~

For this reason it was decided to use a "two stage" bioequivalence study design, that allows a re-calculation of the sample size in case the number of subjects initially enrolled in the study is not large enough to provide a reliable answer to the questions addressed due to underestimation of the variability or misleading estimation of the point estimate for the T/R ratio of the geometric means.

The sample size of stage 1 was calculated assuming a point estimate for the T/R ratio of the geometric means of 1.053 (i.e. $\mu_R=0.95\cdot\mu_T$) and a multiplicative coefficient of variation (CVm) of 20% for both AUC_{0-t} and C_{max}. A power of 90% was considered and, according to the Pocock spending function and to the current European bioequivalence guideline, the α level was set to 0.0294. Fifteen (15) subjects per sequence (i.e. 30 subjects overall) will be enrolled in the first stage of the study.

After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should bioequivalence be proven with the results of the subjects of the first stage ~~**and with an *a posteriori* calculated power of at least 80%**~~, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage **and with an *a posteriori* calculated power > 90% for both AUC_{0-t} and C_{max}, the study will be stopped and the bioequivalence will not be proven.** ~~**or should it be proven with an *a posteriori* calculated power lower than 80%**~~ **Should bioequivalence not be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power ≤ 90% for AUC_{0-t} or C_{max}**, the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. ~~**The Sponsor will decide whether the study has to continue or not. In the first case, t**~~The additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages. The second stage will be performed after notification of the sample size to the local Ethics Committee and to the central Swiss authority (Swissmedic).

…

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 10.2 "Sample size and power considerations" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

In a first study stage 30 healthy volunteers (at least 12 subjects per sex) will be included and treated to receive both test and reference investigational product according to the cross-over design. Drop-out subjects will not be replaced. After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should bioequivalence be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power of at least 80%, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage or should it be proven with an *a posteriori* calculated power lower than 80%, the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. The Sponsor will decide whether the study has to continue or not. In the first case, the additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages.

AMENDED TEXT:

The sample size of stage 1 was calculated assuming a point estimate for the T/R ratio of the geometric means of 1.053 (i.e. $\mu_R=0.95\cdot\mu_T$) and a multiplicative coefficient of variation (CVm) of 20% for both AUC_{0-t} and C_{max}. A power of 90% was considered and, according to the Pocock spending function and to the current European bioequivalence guideline, the α level was set to 0.0294. Fifteen (15) subjects per sequence (i.e. 30 subjects overall) will be enrolled in the first stage of the study.

Table 10.2.1 Stage 1 - Sample size calculation data

PK Parameter	Alpha (one-sided)	μ_T/μ_R	CVm	sqrt(MSE)	Power	N per sequence	Sample size
AUC_{0-t}	0.0294	1.053	20%	0.198	90%	15	**30**
C_{max}	0.0294	1.053	20%	0.198	90%	15	**30**

In a first study stage 30 healthy volunteers (at least 12 subjects per sex) will be included and treated to receive both test and reference investigational product according to the cross-over design. Drop-out subjects will not be replaced. After the end of study stage 1, PK parameters will be calculated and an *ad interim* bioequivalence test will be performed on the calculated PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. To safeguard the overall type I error, the Pocock spending function will be used to determine the α level of the bioequivalence test. Should

bioequivalence be proven with the results of the subjects of the first stage ~~**and with an *a posteriori* calculated power of at least 80%**~~, the primary objective of the study would then be satisfied and the second study stage will not take place. Should bioequivalence not be proven with the results of the subjects of the first stage **and with an *a posteriori* calculated power > 90% for both AUC_{0-t} and C_{max}, the study will be stopped and the bioequivalence will not be proven.** ~~**or should it be proven with an *a posteriori* calculated power lower than 80%**~~ **Should bioequivalence not be proven with the results of the subjects of the first stage and with an *a posteriori* calculated power ≤ 90% for AUC_{0-t} or C_{max},** the overall sample size for the study (stage 1 plus 2) will be calculated on the basis of the *ad interim* bioequivalence results. ~~**The Sponsor will decide whether the study has to continue or not. In the first case, t**~~**T**he additional subjects will be enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test will be performed on the pooled subjects of the two study stages.

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, page 1 and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

Dompé s.p.a.
Via Campo di Pile, 67100 L'Aquila
Milan offices:
Via Santa Lucia 6, 20122 Milano - Italy
Phone: +39.02.58383.1
Fax: +39.02.58383.324
Email: mauro.ferrari@dompe.it

AMENDED TEXT:

~~**Dompé s.p.a.**~~ **Dompè farmaceutici s.p.a**
Milan offices:
Via Santa Lucia 6, 20122 Milano - Italy
Phone: +39.02.58383.1
Fax: +39.02.58383.324
Email: mauro.ferrari@dompe.it
L'Aquila Officies
Via Campo di Pile, 67100 L'Aquila

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 11.7 "Reporting" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

Dompé Medical Expert
Elisabetta Grillo,
Email to: elisabetta.grillo@dompe.it
or Fax: +39.02.58383297

AMENDED TEXT:

Dompé Medical Expert
~~**Elisabetta Grillo**~~, **Federico Saibene**
Email to: ~~**elisabetta.grillo@dompe.it**~~ **federico.saibene@dompe.it**
or Fax: +39.02.58383297

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 16.1 "Sponsor Representative" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

Medical Expert
Elisabetta Grillo, MD
Email: elisabetta.grillo@dompe.it

AMENDED TEXT:

Medical Expert
~~**Elisabetta Grillo**~~ **Federico Saibene**, MD
Email: ~~**elisabetta.grillo@dompe.it**~~ **federico.saibene@dompe.it**

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 13.1 "Monitoring" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

The monitoring visits will be conducted by appropriate staff of Clinical Medical Service Sagl, Switzerland.

AMENDED TEXT:

The monitoring visits will be conducted by appropriate staff of Clinical Medical Service**s** ~~**Sagl**~~ **di Maria Pia Savorelli**, Switzerland.

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 16.5 "Co-ordination, data analysis & reporting" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

Coordination
Angelo Vaccani, PhD, Clinical Project Leader
Email: angelo.vaccani@croalliance.com

Pharmacokinetic Analysis
Luca Loprete, MSc, Senior Pharmacokineticist
Email: luca.loprete@croalliance.com

Biometry Unit Representative
Matteo Rossini, Biometry Manager, MSc, Unit Head
Email: statistics@croalliance.com

Quality Assurance Unit Representative
Maurizio Cuocolo, PharmD, Quality Assurance
Email: qau@croalliance.com

AMENDED TEXT:

Coordination
Angelo Vaccani, PhD, Clinical Project Leader
Email: angelo.vaccani@croalliance.com

Medical Writing
Chiara Leuratti, Medical Writer Manager, Unit Head
Email: medicalwriting@croalliance.com

Pharmacokinetic Analysis
Luca Loprete, MSc, Senior Pharmacokineticist
Email: luca.loprete@croalliance.com

Biometry Unit Representative
Matteo Rossini, Biometry Manager, MSc, Unit Head
Email: statistics@croalliance.com

Quality Assurance Unit Representative
Maurizio Cuocolo, PharmD, Quality Assurance
Email: qau@croalliance.com

AMENDED DOCUMENTS:

Study protocol, Final version 1.0, 28JUL2014, § 16.6 "Monitoring" and any other affected section of the synopsis and protocol.

ORIGINAL TEXT:

Clinical Medical Service Sagl
Via Collina Azzurra 8, CH-6900 Paradiso, Switzerland
Legal address: Via Motta 24, CH-6830 Chiasso, Switzerland
Mobile: +41.79.827.27.67
Fax: +41.91.649.57.14
Email: cmed@cmed.ch

AMENDED TEXT:

Clinical Medical Service**s ~~Sagl~~ di Maria Pia Savorelli**
~~Legal address: Via Motta 24, CH-6830 Chiasso, Switzerland~~
Via Indipendenza 29/A, CH-6883 Novazzano, Switzerland
Mobile: +41.79.827.27.67
Email: cmed@cmed.ch

Signatures for Approval:

SPONSOR
Dompé s.p.a., Italy

Clinical Development Manager
Mauro Paolo. Ferrari, PharmD

02 DEC 2014 _____
Date

_____
Signature

Research & Development Director
Marcello Allegretti, ChemD

02 dec 2014 _____
Date

_____
Signature

INVESTIGATOR(S)

Principal Investigator
I have read this amendment and agree to conduct this trial in accordance with all the stipulations of the protocol and in accordance with the Declaration of Helsinki.

Milko Radicioni, MD
Cross Research Phase I Unit, Switzerland

25 NOV 2014
Date

Signature

CRO
CROSS S.A., Switzerland, and its affiliated companies CROSS Research S.A. and CROSS Metrics S.A.

Coordination
Angelo Vaccani, PhD, Clinical Project Leader

25NOV2014 — Angelo Vaccani
Date — Signature

Pharmacokinetic Analysis
Luca Loprete, MSc, Senior Pharmacokineticist

25NOV2014 — Luca Loprete
Date — Signature

Biometry Unit Representative
Matteo Rossini, MSc, Biometry Manager, Unit Head

25 NOV 2014 — Matteo Rossini
Date — Signature

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

25 nov 2014 — Mario Corrado
Date — Signature