Study 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

STATISTICAL ANALYSIS PLAN

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
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Development phase:	Phase I
Version and date:	Final version 1.0, 13FEB2015

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

This document comprises 22 pages

STATISTICAL ANALYSIS PLAN APPROVAL

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Dompé farmaceutici s.p.a., Italy

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16 FEB 2015 — Date
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LIST OF ABBREVIATIONS

β-HCG	Human Chorionic Gonadotropin β
λ_z	Terminal elimination rate constant
AE	Adverse Event
ANOVA	Analysis of Variance
ASA	Acetylsalicylic Acid
ATC	Anatomical Therapeutic Chemical
AUC0-t	Area under the concentration-time curve from administration to the last observed concentration time t
AUC0-∞	Area under the concentration-time curve extrapolated to infinity
BE	Bioequivalence
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
BT	Body Temeperature
CI	Confidence Interval
Cmax	Maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically Significant
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ETV	Early Termination Visit
F_{rel}	Relative Bioavailability
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IUD	Intra-Uterine Device
KLS	Ketoprofen Lysine Salt
MedDRA	Medical Dictionary for Regulatory Activities
N	Normal
NC	Not calculated
NCS	Not clinically significant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
PK	Pharmacokinetic
PR	Pulse Rate
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R	Reference
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
T	Test
TEAE	Treatment-Emergent Adverse Event
$t_{1/2}$	Half-life
t_{max}	Time to achieve C_{max}
USDA	United States Department of Agriculture
WHODDE	World Health Organisation Drug Dictionary Enhanced

1 INTRODUCTION

The present Statistical Analysis Plan (SAP) has been compiled by the Biometry Unit of the Clinical Contract Research Organization (CRO) based on the study protocol version 1.0 issued on 28JUL2014 and on protocol amendment nr. 1 version 2.0 issued on 25NOV2014. The SAP was reviewed by the Sponsor and finalised before database lock.

1.1 Changes with respect to the study protocol

The amendment nr. 1 version 2.0 issued on 25NOV2014 introduced the following changes with respect to the statistical part of the study protocol (1, 2, 3):

- 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 sample size for study stage 1, the *a posteriori* power analysis in case the bioequivalence is proved with the results of the subjects of the first stage, is not necessary and has been removed
- The stopping criteria of the study have been amended in order to avoid uncontrolled inflation of type I error caused by the enrolment of a too high number of subjects in study stage 2 (overpowered bioequivalence).

2 STUDY DESCRIPTION

2.1 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.

2.1.1 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 (T) and reference (R).

2.1.2 Secondary end-points

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

2.2 Overall study design

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

2.3 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) (4, 5).

Considering the lack of information about the PK profile of the new formulation 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 for study 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) were enrolled in the first stage of the study.

After the end of study stage 1, PK parameters were calculated and an *ad interim* bioequivalence test was 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 was used to determine the α level of the bioequivalence test (see § 6.2).
Should bioequivalence be proven with the results of the subjects of the first stage, the primary objective of the study would then be satisfied and the second study stage will not take place.

Should bioequivalence NOT have been 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 would have been stopped without any further analysis.
Should bioequivalence NOT have been 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) would have been calculated on the basis of the *ad interim* bioequivalence results. The additional subjects would have been enrolled into the second study stage. After completion of stage 2, the PK analysis and the bioequivalence test would have been performed on the pooled subjects of the two study stages. The second stage if applicable, was to be performed only 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 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 § 4.1).

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

For details on the study schedule see below (TABLE 1).

TABLE 1. 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 was performed at screening visit. The same analysis was 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 lunch was served at approximately 5 h post-dose. A standardised light and low-fat dinner were served on day -1 of each period
7: AEs were 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 underwent a final visit. In case of discontinuation, subjects underwent an ETV
9: At visit 2 only

3 STUDY POPULATION

3.1 Target population

The first study stage population included 30 healthy volunteers (at least 12 subjects per sex) aged 18-55 years inclusive.

3.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all of 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.

3.3 Exclusion criteria

Subjects meeting any of these criteria were not 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

3.3.1 Not allowed treatments

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

3.3.2 Allowed treatments

Paracetamol was allowed as therapeutic counter-measure for adverse events (AEs) according to the investigator's opinion. Hormonal contraceptives were allowed too.
The intake of any other medication was reported as a protocol deviation. However, it led to subject's discontinuation from the study only if the investigator, together with the sponsor, considered it could affect the study assessments or outcome.

4 ASSIGNMENT OF STUDY TREATMENT

4.1 Randomisation

The randomisation list was computer-generated by the CRO Biometry Unit, using the PLAN procedure of SAS® version 9.3 (TS1M1) (7) or higher (the actual version will be stated in the final report). The randomisation list was supplied to the study site before study start. The randomisation list will be attached to the final clinical study report.

4.2 Treatment allocation

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

4.3 Blinding

This is an open study. No masking procedure was applied.

5 EVALUATION PARAMETERS

5.1 Study variables

5.1.1 Primary variables

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

5.1.2 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.

5.2 Pharmacokinetic assessments

5.2.1 Pharmacokinetic parameters

The following PK parameters were measured and/or calculated for ketoprofen, using the validated software Phoenix WinNonlin® version 6.3 (8) 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 $R^2 > 0.8$.

5.3 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.

6 STATISTICAL METHODS

The data documented in this study and the parameters measured are 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 are evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (7) or higher (the actual versions will be stated in the final report).
The statistical analysis of PK parameters was performed using Phoenix WinNonlin® version 6.3 (8) or higher and SAS® version 9.3 (TS1M1) or higher.

6.1 Analysis sets

6.1.1 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 was performed through randomised allocation to a 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 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.

6.1.2 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 $AUC_{0-\infty}$.

No subject was excluded from the PK set in the interim analysis and no subject will be excluded from the PK set in the final analysis.

6.2 Sample size and power considerations

This is a two-stage study (see also § 2.2 and 2.3).

6.2.1 Stage 1

The sample size for 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) were enrolled in the first stage of the study. Sample size calculation data are reported in the following table:

Table 6.2.1 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) were included and treated to receive test and reference investigational products according to the cross-over design. Drop-out subjects were not to be replaced.

6.2.2 Whole study

After the end of study stage 1, PK parameters were calculated and an *ad interim* bioequivalence test was 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 was used to determine the α level of the bioequivalence test.

Should bioequivalence be proven with the results of the subjects of the first stage, the primary objective of the study would then be satisfied and the second study stage will not take place.

It was planned that, should bioequivalence NOT have been 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 would have been stopped and the bioequivalence not further investigated. Should bioequivalence NOT have 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) would have been calculated on the basis of the *ad interim* bioequivalence results. The additional subjects would have been enrolled into the second study stage. The second stage, if applicable, would have been performed only after notification of the sample size to the local Ethics Committee and to the central Swiss authority (Swissmedic). After completion of stage 2, the PK analysis and the bioequivalence test would have been performed on the pooled subjects of the two study stages.

6.3 Demographic and other baseline 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.

6.3.1 Subjects' disposition

The disposition of all subjects enrolled in the study will be listed and summarised. The number and percentage of subjects completing the study, the number and percentage of withdrawals and the reasons for withdrawal will be presented.

6.3.2 Analysis sets

The subjects included in each analysis set will be listed and summarised.

6.3.3 Demography

Demographic data will be listed and summarised. The number and percentage of subjects in each category of categorical variables (e.g. sex) and the descriptive statistics (mean, SD, CV%, minimum, median and maximum) of continous variables (e.g. age) will be presented.

6.3.4 Protocol deviations

All the protocol deviations reported during the clinical trial will be listed and summarised. The number and percentage of subjects for each deviation will be reported.

6.3.5 Discontinued subjects

All subjects who discontinue the clinical trial will be listed.

6.3.6 Subjects excluded from the PK analysis

All subjects excluded from the primary PK analysis will be listed and the reasons for exclusion will be reported.

6.3.7 Medical and surgical history

All the findings of medical and surgical history of all subjects enrolled in the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 and listed.

6.3.8 Prior and concomitant medications

Prior and concomitant medications/therapies will be listed and summarised as number of subjects being treated with any type of medication/therapy classified according to the standardised product name of the World Health Organization (WHO) Drug Dictionary

Enhanced (WHODDE version September 1, 2014) and to the Anatomical Therapeutic Chemical (ATC) classification system.

6.3.9 Subjects study visits

The dates of all subjects study visits will be listed.

6.3.10 Tests

The test performance dates and the results of the alcohol breath test and pregnancy test will be listed.

6.3.11 Meals

The dates and times of meals will be listed by treatment.

6.4 Analysis of pharmacokinetic parameters

6.4.1 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.

6.4.2 Statistical comparison of pharmacokinetic parameters

According to the current European Bioequivalence Guideline (1) and European Questions & Answers document (5), PK parameters AUC_{0-t}, $AUC_{0-\infty}$ (if feasible) and C_{max} were analysed using analysis of variance (ANOVA). Before analysis, the data were transformed using a neperian logarithmic transformation. For stage 1 data the statistical analysis took into account treatment, period, sequence and subject (sequence) as sources of variation.

For the analysis (stage 1 data) acceptance criterion for bioequivalence (BE) is a 94.12% confidence interval for the T/R ratio of the geometric means of the parameters within the 80-125% range, according to the current guidelines for BE studies and to the Pocock α spending function.

If the study is terminated after the interim analysis (see § 6.2), the interim analysis will be regarded and presented in the CSR as the final data analysis.

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

6.5 Interim analysis at the end of the study stage 1

An ad interim bioequivalence test on the available PK data was performed at the end of stage 1, as described in paragraphs § 2.3 and § 6.2.

The pharmacokinetic and statistical analysis on the first study stage data was completed on 09FEB2015. According to the current European Bioequivalence Guideline (1), 94.12% confidence intervals (Pocock correction was applied) were calculated for PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the 30 randomised subjects. The CIs corresponded to 97.57-119.81% for C_{max}, 104.26-117.38% for AUC_{0-t} and 104.35-117.41% for $AUC_{0-\infty}$ and were inside the 80.00-125.00 limits for all parameters.

Bioequivalence was proven with the results of the subjects of the first stage, the primary objective of the study is satisfied and the second study stage will not take place.

6.6 Safety evaluation

6.6.1 Adverse events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
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 in tables of frequency. The number and percentage of subjects with any TEAE, the number of TEAEs, the number and percentage of subjects with any TEAE by severity, the number of TEAEs by severity, the number and percentage of subjects with any TEAE related to study drug and the number of TEAEs related to study drug will be presented.

Serious TEAEs will be summarized by treatment. Should any serious TEAE occur, the number and percentage of subjects with any serious TEAE, the number of serious TEAEs, the number and percentage of subjects with any serious TEAE related to study drug and the number of serious TEAEs related to study drug will be presented.

All TEAEs leading to death, Serious TEAEs and TEAEs leading to discontinuation will be listed, if occurring.

6.6.2 Physical examination

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

6.6.3 Laboratory data

Date/time of samples collection and overall investigator's interpretation (as normal [N], abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF and listed in the final clinical study report. The Investigator's interpretations will be summarised by tables of frequency.

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.

6.6.4 Vital signs

Values of vital signs will be listed and summarised by descriptive statistics. Changes from baseline (pre-dose assessment) will be summarised by descriptive statistics.

6.6.5 Body weight

Values of body weight will be listed and summarised by descriptive statistics. Changes from baseline (screening assessment) will be summarised by descriptive statistics.

6.6.6 ECGs

Date of ECG recording and overall investigator's interpretation (as normal [N], abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF and listed in the final clinical study report. The Investigator's interpretations will be summarised by tables of frequency.

Hard copies of the ECGs will be attached to the CRF. All clinically significant abnormalities after the screening visit will be recorded as AEs.

6.6.7 Drug administration

The extent of exposure (i.e. dose and dose/body weight) will be listed and summarised by descriptive statistics. The actual date/time of each drug administration and the start date/time of fasting conditions will be listed.

7 REFERENCES

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5. Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party. EMA/618604/2008 Rev. 8, 10 October 2013
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