Statistical Analysis Plan

BI trial Number: 0107-0277

project code: 17BI01

Protocol Title: An open-label, randomised, single-dose, two-way crossover study in healthy male and female volunteers to evaluate the relative bioavailability of a new oral formulation of meloxicam, Movalis® capsules 15 mg, versus Movalis® tablets 15 mg, after administration under fasting state.

Effective date: 06 May 2019

Version No.: 1.0 dated 06 May 2019

CHANGE HISTORY

Version	Date	Description	Author
1.0	06 May 2019	New version	

SIGNATURES

Author:

_____ _____

Signature Date

Name: _____

Position: Data manager

Approved:

_____ _____

Signature Date

Name:_____

Position: Head of the Data Management Department

Approved:

_____ _____

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Name:_____

Position: Bioequivalence studies Project Manager

Approved (Sponsor):

_____ _____

Signature Date

Name: _____

Position: Project Manager

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1. Study Rationale

1.1. Introduction

This document contains Summary Results Plan (descriptive statistics) and Statistical Analysis Results of a clinical bioequivalence study. The clinical report on the results of this clinical study will mainly be based on the results of the statistical analysis designed in this document.

1.2. Study Hypothesis and Preliminary Data

The bioequivalence of Movalis® capsules 15 mg versus Movalis® tablets 15 mg, is established by average bioequivalence method to make sure that the coefficient of PK parameters (AUC_{0-t} or $AUC_{0-\infty}$ and C_{max}) of both treatments (T/R) is within the specified acceptable range. The acceptable range for geometric mean ratio is 80-125% for AUC_{0-t} and 80-125% for C_{max} [1].

Check the equivalence hypothesis:

- Null hypothesis on the no equivalence (H_0): $\mu T-\mu R \leq -\delta$ or $\mu T-\mu R \geq \delta$ (i.e. the difference in the average population responses is less than or equal to the lower limit, or higher than or equal to the upper limit of the acceptable range).
- Alternative hypothesis on the bioequivalence (H_A): $-\delta < \mu T-\mu R < \delta$ (i.e., the difference of the average population responses is higher than the lower limit and less than the upper limit of the acceptable range), where μT and μR are the average responses of the population of log-transformed values for dosage forms T (Movalis® capsules 15 mg) and R (Movalis® tablets 15 mg), and δ is the bioequivalence limit that determines the acceptable range for AUC_{0-t} or $AUC_{0-\infty}$ and C_{max} on logarithmic scale.

In this study, e.g., δ is taken for ln(1.25) to compare AUC. This corresponds to an acceptable range of 80 to 125% for the geometric mean ratio of parameters on the original scale.

This hypothesis and its alternative can be divided into two one-sided null hypotheses, H_{01} and H_{02}, with the concomitant alternatives:

H_{01}: $\mu T-\mu R \leq -\delta$ versus H_{A1}: $\mu T-\mu R > -\delta$

H_{02}: $\mu T-\mu R \geq \delta$ versus H_{A2}: $\mu T-\mu R < \delta$

Due to the nature of the confidence intervals obtained under the test of hypothesis on normal distribution, the test of null hypothesis at $\alpha = 0.05$ is equivalent to two one-sided tests of the above null hypotheses, each with $\alpha = 0.05$ significance level. The deviation of both null hypotheses H01 and H02 at $\alpha = 0.05$ is equivalent to the inclusion of 90% confidence interval for μT-μR in the acceptable range.

1.3. Protocol Synopsis

Study ID:	0107-0277
Protocol version and date:	Version: 1.0 dated May 28, 2018
BI Study ID:	0107-0277
Protocol amendments:	Not applicable
Protocol title:	An open-label, randomised, single-dose, two-way crossover study in healthy male and female volunteers to evaluate the relative bioavailability of a new oral formulation of meloxicam, Movalis® capsules 15 mg, versus Movalis® tablets 15 mg, after administration under fasting state.

Principal Investigator:	. Address: Phone: Fax:
Study site:	Address:
Study phase:	Bioequivalence study
Objectives:	Primary objective: Study relative bioavailability of Movalis® capsules 15 mg, versus Movalis® tablets 15 mg. Secondary objectives: 1. Establish the bioequivalence of Movalis® capsules 15 mg, and Movalis® tablets 15 mg. 2. Evaluation of safety and tolerability is an additional study objective.
Methodology:	It will be an open-label, randomised, two-way crossover study with a single dose of medicinal products taken by healthy male and female volunteers under fasting state, conducted in the clinical study site located in the Russian Federation.
Number of subjects:	26
Test drug:	Movalis® capsules 15 mg (T)
Reference drug:	Movalis® tablets 15 mg (R)
Number of subjects in each group:	Movalis® capsules 15 mg (Test drug, T) – 26, Movalis® tablets 15 mg (Reference drug, R) – 26
Diagnosis:	Not applicable
Duration of study participation:	Not more than 32 days.
Main inclusion criteria:	Male and female subjects aged 18-45 years old, inclusive. Body mass index according to the Quetelet index in the range of 18.50 – 29.99 kg/m^2, inclusive.
Pharmacokinetics criteria:	Primary endpoints: AUC_{0-t} and $C_{max.}$ Secondary endpoints: $AUC_{0-\infty}$.
Safety criteria:	Vital signs (blood pressure, pulse rate, body temperature, respiratory rate), performance status, physical examination, 12-lead ECG, laboratory tests, adverse events.

Statistical methods:	Two-sided 90% confidence intervals for the intra-individual ratio (according to geometric mean) for each of the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} indices will be calculated to determine if confidence intervals enter acceptable bioequivalence range (80-125% for AUC_{0-t}; 80-125% for C_{max}). ***The drugs will be considered bioequivalent:*** • if the limits of the estimated confidence interval for AUC_{0-t} are within the range of 80.00–125.00%; • if the limits of the estimated confidence interval for C_{max} are within the range of 80.00–125.00%. As a statistical model, analysis of variance (ANOVA) for log-transformed parameters will be used, including such effects as "sequences", "study subjects grouped within a sequence", "period" and "type of therapy". Confidence intervals will be calculated according to the residual error obtained in the ANOVA analysis of variance. The effect of "study subjects grouped within a sequence" will be considered random, while other effects are fixed. The descriptive statistics values will be calculated for all other parameters.

2. Study Goals

Primary objective:

- Study relative bioavailability of Movalis® capsules 15 mg, versus Movalis® tablets 15 mg.

Secondary objectives:

- Establish the bioequivalence of Movalis® capsules 15 mg, and Movalis® tablets 15 mg.
- Evaluation of safety and tolerability is an additional study objective.

3. Study Endpoints

3.1. Primary Endpoints

Relative bioavailability should be studied primarily under the following pharmacokinetic parameters:

- AUC_{0-t} (the area under the concentration-time curve of the analyte in plasma over the interval from 0 to the last quantifiable data point).
- C_{max} (maximum measured concentration of the analyte in plasma).

3.2. Secondary endpoints

The following secondary endpoints will be evaluated:

Pharmacokinetic parameters:

- $AUC_{0-\infty}$ (the area under the concentration-time curve of the analyte in plasma over the interval from 0 with extrapolation to infinity).

4. Study Design

This is an open-label, single-dose, randomised, two-way crossover study. Study subjects will be randomly assigned to one of two treatment sequences

4.1. Number of comparison groups

Two comparison groups:

• Movalis® capsule 15 mg,

• Movalis® tablet 15 mg

4.2. Number of centers

This clinical study is planned to be conducted in one clinical center:

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4.3. Masking type

Not applicable.

4.4. Randomization

Subjects will be randomized to one of two treatment sequences at ratio of 1:1. CRO will determine the randomization scheme (make a randomization list). A randomization list will be created using a validated system that includes a pseudo-random number generator and the provision of random numbers so that the number distribution to subjects is reproducible and unpredictable.

4.5. Control method

Not applicable.

4.6. Inclusion Criteria

1. Men and women aged 18–45 years old, inclusive.
2. Body mass index according to the Quetelet index in the range of 18.50–29.99 kg/m2, inclusive.
3. The verified diagnosis “healthy” as concluded by the Investigator according to the medical history, results of the physical examination, ECG, vital signs (blood pressure, heart rate, respiratory rate and body temperature), and laboratory parameters.
4. Preliminary standard clinical and laboratory studies and investigations did not reveal any diseases or abnormalities.
5. Systolic blood pressure is not less than 100 mmHg and not higher than 139 mmHg; diastolic blood pressure is not less than 70 mmHg and not more than 90 mmHg; heart rate is not less than 60 bpm and not more than 90 bpm, respiratory rate is within 12-20 per minute.
6. Ability to understand and accept study rationale; available written informed consent of the volunteer to participate in the study in accordance with the applicable law.

7. For females with preserved reproductive potential: a negative pregnancy test and consent to adhere to adequate contraceptive methods from a screening visit to 30 days after the last dose of the test drug, inclusive. If a woman is postmenopausal (no menstruation for at least 1 year) or she underwent surgical sterilization (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), she is not eligible for this requirement. If oral contraceptives are used, they should be withdrawn at least 2 months before study initiation.
8. For males: consent to adhere to adequate contraceptive methods (barrier methods of contraception) from a screening visit to 30 days after the last dose of the test drug, inclusive.

4.7. Non-inclusion criteria

1. Drug intolerance to any medicinal product.
2. Positive history of allergies.
3. Acute infectious diseases or allergic reactions that require treatment (including drug allergy), less than 4 weeks before the first day of screening.
4. Gastrointestinal surgeries (except of appendectomy), which can significantly affect absorption or metabolism of the investigational products.
5. Volunteers with known hypersensitivity to meloxicam or any excipient of the test drug or reference drug.
6. Known hypersensitivity to NSAIDs: volunteers who developed signs of bronchial asthma, nasal polyps, angioedema or urticaria after administration of acetylsalicylic acid or other NSAIDs.
7. Chronic diseases of cardiovascular, bronchopulmonary, neuroendocrine system, as well as gastrointestinal, hepatic disorders, kidney diseases, blood disorders or other conditions that does not allow a volunteer to participate in the study as concluded by the Investigator.
8. Results of standard laboratory tests and investigations obtained during the screening that are outside the normal limits.
9. History of ulcers/GI perforations or bleeding; history of malignancies within 5 years prior to the screening period.
10. Positive blood test results for infectious diseases (HIV, syphilis, hepatitis B or C) at screening.
11. Positive breath alcohol test at screening.
12. Positive urine drug screen for narcotic and potent substances (marijuana, benzodiazepine, barbiturates, opiates, cocaine and amphetamine) at screening.
13. Pregnancy or breastfeeding.
14. Any diet, e.g., vegetarian within 2 weeks before the first day of screening.
15. Ingestion of more than 10 units of alcohol per week (1 unit of alcohol is equivalent to ½ liter of beer, 200 mL of wine or 50 mL of alcohol) or history of alcoholism, drug addiction or abuse of medicinal products.
16. Impossibility to get along without food for at least 12 hours and inability for drug administration under fasting conditions.
17. Blood donation (450 mL of blood or plasma and more) within 3 months before screening.

18. Depot injections, installation of intrauterine hormonal therapeutic systems or implants of any medicinal products 6 months prior to screening.
19. For females: use of hormonal contraceptives less than 2 months before screening.
20. Regular drug administration less than 2 weeks before screening.
21. Administration of medicinal products that have a pronounced effect on liver function, etc. (barbiturates, omeprazole, cimetidine, etc.), within 4 weeks before screening.
22. For females: volunteers with preserved reproductive potential who had unprotected intercourse with an unsterilized male partner within 30 days prior to screening.
23. Participation in any other clinical study or administration of investigational products within 3 months before screening.
24. Difficult venous access which complicates or prevents the installation of a catheter and frequent blood draws.
25. Smoking (≥10 cigarettes or ≥ 3 pipes daily).
26. Inability to refrain from smoking during the study.
27. Volunteers who do not want or are unable to give up alcohol and vigorous exercises from the first day of screening to the follow-up visit.
28. Volunteers who do not want or are unable to refuse drinks or food containing methylxanthines (coffee, tea, cola, energy drinks, chocolate, etc.), as well as grapefruit/grapefruit juice, bitter orange (marmalade) and its juice, food additives and products, including St. John's wort (Hypericum perforatum), from the first day of screening to the follow-up visit.
29. Volunteers with a lifestyle (including night work and extreme physical activities such as sports or weight lifting), which can interfere the interpretation of the laboratory data obtained during the study.
30. Volunteers who will not adhere to the study regime.
31. Volunteers who are apparently or likely, as concluded by the Investigator, not able to understand and evaluate the study-related information during ICF signing, in particular regarding the expected risks and possible discomfort.
32. Dehydration in volunteers due to diarrhea, vomiting or other cause within the last 24 hours before the first day of screening.
33. Volunteers with history of seizures, epilepsy and any other neurological disorders.
34. Recent cerebral hemorrhage or proved systemic bleeding disorders.
35. History of lactose intolerance.
36. Reports on difficulty in swallowing tablets or capsules.

4.8. Exclusion criteria

1. A volunteer withdrew the informed consent, and the justification is not required.
2. The Investigator decided that the volunteer should be excluded for the benefit of the volunteer himself/herself.

3. Non-compliance with non-inclusion criteria revealed during the study. Abnormalities of vital signs, as well as in standard investigations versus normal limits revealed after the volunteer administered the investigational product, are defined adverse events.
4. Emerged AE/SAE when the continuation of volunteer's participation in the study is undesirable or impossible (as concluded by the Sponsor/Manufacturer or Investigator).
5. Vomiting or diarrhea within 12 hours after drug administration.
6. A volunteer should administer concomitant drugs which cannot be used with the test drug, other investigational products, or if any unauthorized medicinal product is to be used concomitantly (Protocol violation).
7. Failure to adhere to the Protocol requirements: the schedule for biosamples collection (2 times and more), the regime throughout the study, including the "washout" period (drinking alcohol, prohibited foods, etc.).
8. A volunteer does not comply with the rules of inpatient stay.
9. A volunteer receives additional treatment (or needs additional treatment), which can affect the pharmacokinetics of the investigational product.
10. A volunteer needs hospitalization during the study.
11. Volunteers visit the hospital after the appointed time (more than 1 hour late) which violates the Protocol requirements.
12. A volunteer has a positive breath alcohol test.
13. A volunteer has a positive pregnancy test.
14. A volunteer has a positive drug screen for narcotic and potent substances (marijuana, benzodiazepine, barbiturates, opiates, cocaine and amphetamines).
15. If the emerged adverse events to the drug are so serious that the continuation of the study is unacceptable.
16. A volunteer has ≥3-fold AST and/or ALT level increase versus ULN together with ≥2-fold increase in total bilirubin versus ULN (measured in the same blood sample) and/or if follow up is required in accordance with section 10.1 of this study Protocol and a "therapeutic and prophylactic meals checklist" is provided to the federal study site.

4.9. Total number of subjects and conditions of distribution to treatment groups

It is planned to enroll 26 healthy male and female volunteers. Volunteers will be randomized (see section 4.4) to one of two treatment sequences:

- TR (Test drug administration in the first study period and Reference drug administration in the second study period).
- RT (Reference drug administration in the first study period and Test drug administration in the second study period).

4.10. Description of intervention

The therapy includes the administration of Movalis®, one capsule 15 mg, under fasting condition, as Test drug (T), and Movalis®, one tablet 15 mg, under fasting condition, as Reference drug (R).

4.10.1. The test drug

Movalis® capsules 15 mg.

INN	Meloxicam
Trade name	Movalis®
Dosage form	Capsules
Active ingredient	Meloxicam 15 mg
Manufacturer	Boehringer Ingelheim Ellas A.E., Greece
Pharmacotherapeutic group	Non-steroidal anti-inflammatory drug

4.10.2. The reference drug

Movalis® tablets 15 mg.

INN	Meloxicam
Trade name	Movalis®
Dosage form	Tablets
Active ingredient	Meloxicam 15 mg
Manufacturer	Boehringer Ingelheim Ellas A.E., Greece and Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Pharmacotherapeutic group	Non-steroidal anti-inflammatory drug

4.10.3. Dosage

Test drug: 1 capsule (15 mg) of Movalis®.

Reference drug: 1 tablet (15 mg) of Movalis®.

4.10.4. Method of administration

Oral administration with 200 mL of water under fasting at night time for at least 10 h.

4.10.5. Duration of administration

Single dose of the test drug and reference drug by each study subject.

4.10.6. Description of study visits and procedures during each visit

Study procedures schedule is described in Appendix 1.

4.10.6.1. Screening and introductory period

Screening procedures are necessary to determine the eligibility of a subject in terms of study inclusion criteria. Screening procedures include the following:

- Demographic data collection;
- Medical history collection (including lifestyle and pernicious habits);
- Medication history collection;
- Measurement of body weight and body height, calculation of body mass index (BMI);
- Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate;
- Physical examination;
- Review of tests for exclusion: serological test of blood plasma to detect infectious diseases, urine pregnancy test, urine drug screen for narcotic and potent substances, breath alcohol test;

- Standard laboratory tests under fasting condition (hematology, blood biochemistry and urinalysis with microscopic examination of urinary sediment);
- 12-lead ECG (if 12-lead ECG is taken between Day -7 and Day -1 (inclusive) at the screening stage, its results can also be used on Day -1, Period I);
- Evaluation of study inclusion/non-inclusion criteria;
- Evaluation of adverse events.

4.10.6.2. Treatment period

Each subject will have two 4-day periods during the treatment phase. The administration of the test drug and reference drug will be separated by a 7-day washout period (about 8 half-lives).

4.10.6.2.1. Period I/Visit 2

Day -1

The following study procedures will be performed before subjects randomization:

- Physical examination.
- Evaluation of adverse events.
- Documenting concomitant medications.
- Assessment of changes in medical history.
- Assessment of adherence to study limitations.
- Review of tests for exclusion: urine pregnancy test, urine drug screen for narcotic and potent substances, breath alcohol test.
- Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate.
- 12-lead ECG (If 12-lead ECG is taken between Day -7 and Day -1 (inclusive) at the screening stage, its results can also be used on Day -1, Period I).
- Performance status.
- Evaluation of inclusion/non-inclusion criteria.

Randomization will be performed on Day -1, after completion of all study procedures. Randomization numbers will be assigned sequentially in ascending order. A randomization number is designated to the study subject throughout the study.

Day 1

Time point from 2 hours before the administration of the investigational product to 1 minute before the administration of the investigational product:	Blood collection for PK before the administration of the investigational product. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Evaluation of adverse events. Documenting concomitant medications.
Timepoint 00:00:	Administration of the investigational product (capsule or tablet) under fasting conditions seated/standing with 200 mL of boiled water having the room temperature.
Timepoint 00:30±0:02 minutes:	Blood collection for PK.
Timepoint 01:00±0:02 minutes:	Blood collection for PK.
Timepoint 02:00±0:02 minutes:	Blood collection for PK.
Timepoint 03:00±0:05 minutes:	Blood collection for PK.
Timepoint 04:00±0:05 minutes:	Blood collection for PK. Breakfast.
Timepoint 05:00±0:05 minutes:	Blood collection for PK.
Timepoint 06:00±0:05 minutes:	Blood collection for PK. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate.

	Evaluation of adverse events. Lunch. Documenting concomitant medications.
Timepoint 07:00±0:10 minutes:	Blood collection for PK.
Timepoint 08:00±0:10 minutes:	Blood collection for PK.
Timepoint 09:00:	Snack.
Timepoint 10:00±0:10 minutes:	Blood collection for PK.
Timepoint 11:00:	Supper.
Timepoint 12:00±0:10 minutes:	Blood collection for PK. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Evaluation of adverse events. Documenting concomitant medications.

Day 2

Timepoint 24:00±0:15 minutes:	Blood collection for PK. Physical examination. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Performance status. Evaluation of adverse events. Documenting concomitant medications.
Timepoint 32:00±0:15 minutes:	Blood collection for PK.

Day 3

Timepoint 48:00±0:15 minutes:	Blood collection for PK. Physical examination. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Performance status. Evaluation of adverse events. Documenting concomitant medications.

Day 4

Timepoint 72:00±0:15 minutes:	Blood collection for PK. Physical examination. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Performance status. Evaluation of adverse events. Documenting concomitant medications. Standard laboratory tests (complete blood count, blood biochemistry and urinalysis with microscopic examination of urinary sediment).

4.10.6.2.2. Period II/Visit 3

Day 7

After the end of hospitalization the following study procedures will be performed:

- Physical examination.
- Evaluation of adverse events.
- Documenting concomitant medications.
- Assessment of changes in medical history.

- Assessment of adherence to study limitations.
- Review of tests for exclusion: urine pregnancy test, urine drug screen for narcotic and potent substances, breath alcohol test.
- Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate.
- 12-lead ECG.
- Performance status.

Day 8

Timepoint from 2 hours before the administration of the investigational product to 1 minute before the administration of the investigational product:	Blood collection for PK before the administration of the investigational product. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Evaluation of adverse events. Documenting concomitant medications.
Timepoint 00:00:	Administration of the investigational product (capsule or tablet) under fasting conditions seated/standing with 200 mL of boiled water having the room temperature.
Timepoint 00:30±0:02 minutes:	Blood collection for PK.
Timepoint 01:00±0:02 minutes:	Blood collection for PK.
Timepoint 02:00±0:02 minutes:	Blood collection for PK.
Timepoint 03:00±0:05 minutes:	Blood collection for PK.
Timepoint 04:00±0:05 minutes:	Blood collection for PK. Breakfast.
Timepoint 05:00±0:05 minutes:	Blood collection for PK.
Timepoint 06:00±0:05 minutes:	Blood collection for PK. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Evaluation of adverse events. Lunch. Documenting concomitant medications.
Timepoint 07:00±0:10 minutes:	Blood collection for PK.
Timepoint 08:00±0:10 minutes:	Blood collection for PK.
Timepoint 09:00:	Snack.
Timepoint 10:00±0:10 minutes:	Blood collection for PK.
Timepoint 11:00:	Supper.
Timepoint 12:00±0:10 minutes:	Blood collection for PK. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Evaluation of adverse events. Documenting concomitant medications.

Day 9

Timepoint 24:00±0:15 minutes:	Blood collection for PK. Physical examination. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Performance status. Evaluation of adverse events. Documenting concomitant medications.
Timepoint 32:00±0:15 minutes:	Blood collection for PK.

Day 10

Timepoint 48:00±0:15 minutes:	Blood collection for PK.

	Physical examination. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Performance status. Evaluation of adverse events. Documenting concomitant medications.

Day 11

Timepoint 72:00±0:15 minutes:	Blood collection for PK. Physical examination. Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate. Performance status. Evaluation of adverse events. Documenting concomitant medications. Standard laboratory tests (complete blood count, blood biochemistry and urinalysis with microscopic examination of urinary sediment). 12-lead ECG.

4.10.6.2.3. Completion of the study and follow-up period

After the completed treatment phase, a follow-up visit for the study subjects will be carried out 7 days after the completion of the last procedure in the second study period.

During the follow-up visit (Day 18) the following procedures will be performed:

- Physical examination.
- Assessment of vital functions: blood pressure, pulse rate, body temperature, respiratory rate.
- Evaluation of adverse events.
- Documenting concomitant medications.
- Urine pregnancy test.

In case of early study termination by the volunteer, a follow-up visit will be 7 days after the last study procedure preceding the subject's termination of the study.

5. Power and Sample Size

Sample size for this study was determined independently using AUC and C_{max} parameters as the basis for study size determination.

The sample size for this study was determined according to 18% intra-individual coefficient of variation (CV) for AUC and 23% for C_{max}, taking into account the data obtained during the study 107.074 [2]. Although intra-individual CV was 12.9% for AUC and 17.9% for C_{max} according to 107.074 study, such data were obtained exclusively from male subjects. Therefore, the intra-individual CV expected under this study (for males and females) will be accepted in the calculations at least 5% higher than previously reported.

With a CV of 18% for AUC and 23% for C_{max}, and a sample size of 24 subjects, the statistical power to reject the null bioequivalence hypothesis for both parameters (AUC and C_{max}) in favor of equivalence at 5% significance level is described in Table 5.1 and Table 5.2 at various acceptable values of the ratio between the geometric mean of the studied parameters.

Table 5.1. The probability of the drug equivalence according to AUC (with 80-125% acceptable equivalence limits), taking into account 18% intra-individual CV and different values of the geometric mean ratio for the studied parameter in the two-way crossover study (N=24)

Ratio[1]	90%	95%	100%	105%	110%
Test power	72%	94%	99%	95%	78%

1) This ratio reflects the median of the intra-subject ratio determined by exp (μT)/exp (μR) and is calculated as the geometric mean of the intra-subject ratio.

Table 5.2. The probability of the drug equivalence according to C_{max} (with 80-125% acceptable equivalence limits), taking into account 23% intra-individual CV and different values of the geometric mean ratio for the studied parameter in the two-way crossover study (N=24)

Ratio[1]	90%	95%	100%	105%	110%
Test power	54%	81%	90%	82%	60%

1) This ratio reflects the median of the intra-subject ratio determined by exp (μT)/exp (μR) and is calculated as the geometric mean of the intra-subject ratio.

In accordance with the instructions for bioavailability/bioequivalence studies in the Russian Federation, the minimum required number of healthy volunteers is 18 [3]. Below are the tables (Tables 5.3 and 5.4) to demonstrate what is the likelihood of equivalence of the test drug and the reference drug under AUC and C_{max} parameters providing the participation of 18 healthy volunteers.

Table 5.3. The probability of the drug equivalence according to AUC (with 80-125% acceptable equivalence limits), taking into account 18% intra-individual CV and different values of the geometric mean ratio for the studied parameter in the two-way crossover study (N=18)

Ratio[1]	90%	95%	100%	105%	110%
Test power	60%	87%	95%	87%	66%

1) This ratio reflects the median of the intra-subject ratio determined by exp (μT)/exp (μR) and is calculated as the geometric mean of the intra-subject ratio.

Table 5.4. The probability of the drug equivalence according to C_{max} (with 80-125% acceptable equivalence limits), taking into account 23% intra-individual CV and different values of the geometric mean ratio for the studied parameter in the two-way crossover study (N=18)

Ratio[1]	90%	95%	100%	105%	110%
Test power	43%	67%	76%	68%	48%

1) This ratio reflects the median of the intra-subject ratio determined by exp (μT)/exp (μR) and is calculated as the geometric mean of the intra-subject ratio.

From the above tables (Table 5.1 and Table 5.2), a sample size of 24 subjects will provide at least 80% of the test power to conclude bioequivalence of drugs if the geometric mean ratio of the studied parameters (AUC and C_{max}) at least 5% differs from complete equivalence (i.e. 100%). Taking into account 2 cases of dropout, it is planned to include 26 subjects in the study.

Calculations have been made for individual comparisons as described by et al [4] using the power.TOST () command from the PowerTOST package, version 1.2-03 in R version 3.0.3.

6. Data Management Procedures

6.1. Study Database

The electronic data collection system Cloud solution EDC2GO will be used for data collection. Provider: Genae

The database will be developed based on the paper template CRF. The Data Entry Specialist who has the appropriate rights in the database will perform data entry in the office of the CRO. All study data will be validated according to the Data Validation Plan. Requests for data clarification will be created during the data validation. The database will be closed after all the required checks are performed and all queries are resolved. A detailed description of the processing steps is provided in the Data Management Plan

6.2. Study Datasets

Descriptions of the study data sets are described in Appendix 3

6.3. Data Modifications

Data modification is not planned (not applicable).

6.4. Blinding and Randomization.

SAS package version 9.3 will be used for randomization schedule creation. Masking data is not planned (not applicable).

6.5. Unblinding Methods and Procedures

Not applicable.

7. Study Populations

7.1. Safety Population (SP)

All subjects who received at least one dose of the investigational product will be included in the safety assessment. Safety studies will be carried out in accordance with the Boehringer Ingelheim standards.

Data from volunteers who were not randomized in the study and who did not take any dose of the test drug or the reference drug will be provided separately.

7.2. Pharmacokinetic population (PKP)

Pharmacokinetic population is defined as all volunteers who completed the study in accordance with the requirements of the clinical study Protocol for whom the pharmacokinetic profile can be adequately described.

8. Subjects Accountability

Subjects accountability will be carried out with the division into the following groups:

1) Volunteers not included in the studied populations. This group includes:

- Volunteers who signed an informed consent form, but discontinued before the randomization.

2) Volunteers included into the safety population. This group includes:

- Volunteers who underwent randomization and took the test drug and/or the reference drug.
- Volunteers who took at least one dose of trial drug, but early withdrew from the study.
- Volunteers who completed their participation in the study in accordance with the requirements of the clinical study Protocol.

3) Volunteers included into the Pharmacokinetic population. This group includes:

- Volunteers who completed their participation in the study in accordance with the requirements of the clinical study Protocol.

9. Data and values of indicators obtained during the study

9.1. Safety data

All subjects who received at least one dose of the investigational product will be included in the safety assessment. Safety studies will be carried out in accordance with the Boehringer Ingelheim standards.

Analyzed safety parameters include:

- Vital signs (blood pressure, pulse rate, body temperature, respiratory rate);
- Volunteer's performance status;
- Physical examination data;
- Clinical laboratory tests data (complete blood count, blood biochemistry and urinalysis);
- 12-lead ECG data.

9.1.1. Nominal data

Values with a nominative type of the scale will be presented using the total number of observations and the number of observations for each category and percentage. The percentage will be represented with 1 digit after the decimal point.

9.1.2. Interval (quantitative) data

Interval (quantitative) values will be presented using the following values of descriptive statistics: number of observational data except omissions (n), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean and geometric coefficient of variation. The arithmetic mean, standard deviation, minimum and maximum values, and median will be represented in decimal form with the same level of accuracy (the number of digits after the decimal point) as in the initial data.

9.1.3. Handling missing data

Within safety evaluation, no imputation of missing values is planned.

9.2. Pharmacokinetic data

All randomized volunteers who meet the Protocol requirements, e.g., volunteers who meet the inclusion/exclusion criteria and completed the planned periods of investigational product administration in accordance with the Protocol requirement (except for minor deviations that are not a clear basis for exclusion), form a volunteer population "without Protocol deviations" for pharmacokinetic evaluation.

The following volunteers will be included in the pharmacokinetic and statistical analysis:

- Volunteers who have completed all study periods with less than two missing samples.

The calculation will be based on the real, not planned, sampling time.

Decision to exclude the results of analyte concentrations in volunteer's samples will be taken before the final analysis of samples.

If the concentration in a volunteer was less than or equal to 5% of C_{max} before the test drug or the reference drug administration, the data of this volunteer can be included in the pharmacokinetic measurements and calculations without any counting. If the concentration value prior to the test

drug or the reference drug administration is greater than 5% of C_{max}, then this volunteer's data will be excluded from pharmacokinetic and statistical analysis.

Data of volunteers excluded from the analysis due to the concentration value before the drug administration above 5% of C_{max} will be included in a separate Appendix to the final study report.

Volunteers whose reference drug concentration in plasma cannot be determined, or when only a small amount of the drug is detected, will be excluded from pharmacokinetic and statistical analysis. Analyte concentrations in volunteers are considered to be very low if the AUC value does not exceed 5% of the mean geometric AUC of the reference drug (calculated without including volunteer's data with the specified values).

If the value of LLOQ (lower limit of quantification) is more than 5% for C_{max} of a single volunteer, then this volunteer's data will be excluded from pharmacokinetic and statistical analysis. The volunteer's data are included in a separate Appendix of the final study report. During pharmacokinetic and statistical analysis, drug concentrations below the lower limit of quantitation (BLQ) analysis will be counted as zero. Missing samples and non-detectable concentrations (e.g., insufficient amount) from the analytical laboratory will be interpreted in the pharmacokinetic analysis as if they were not collected.

9.2.1. Primary analysis

Main pharmacokinetic parameters will be obtained by analyzing the non-compartmental model using the WinNonlin software (Pharsight, USA).

The pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) will be transformed logarithmically (natural logarithm) before selecting the analysis-of-variance model. The difference between the expected average for the double logarithm of T-R will be estimated upon the difference in the mean values calculated by the least-squares method (point estimation), and also by the difference in the values of the two-sided 90% confidence intervals based on t distribution. These data will then be converted back under the original scale to obtain a point estimation and 90% confidence interval for each endpoint.

All evaluated subjects for both treatment periods will be included in the analysis of relative bioavailability.

Subject is not evaluable if:

- Subject has a Protocol deviation related to the assessment of relative bioavailability (the decision on Protocol deviation relevance will be taken no later than the Report planning meeting) or
- Subject has nausea and vomiting at two mean time t_{max} or less, namely within 12 hours after the administration of the investigational product.

9.2.2. Secondary assays

Concentrations will be used to build charts and perform calculations in the format specified in the analytical report.

Drug concentrations in plasma will be plotted in diagram to a time base for all subjects, as indicated in the concentration-time tables. To demonstrate the average profiles, the arithmetic mean and the specified sampling time will be used.

The following descriptive statistics will be calculated for plasma concentration, as well as for all primary, secondary and additional pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, mean, maximum, arithmetic coefficient of variation, geometric mean and geometric coefficient of variation. Data format for the descriptive concentration statistics will be identical to the data format of the corresponding concentrations. Descriptive statistics of pharmacokinetic parameters will be calculated using individual values with the number of decimal digits provided by the evaluation program. Individual values, as well as descriptive statistics, will then be recorded with three significant figures in the clinical study report.

9.2.3. Dispersion analysis

As a statistical model for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, the analysis of variance (ANOVA) model using the logarithmic scale will be used. This model will include effects taking into account the following sources of variation:

- "Sequence".
- "Study subjects grouped within the sequence".
- "Period".
- "Type of therapy".

The effect of "study subjects grouped within a sequence" will be considered random, while other effects are fixed.

9.2.4. The profile of plasma concentration in the course of time

Concentration data with the NOS (no sample), NOR (no reasonable result), NOA (no sample analyzed), BLQ (below the limit of quantification) and NOP (no peak detectable) label will be identified this way and will not be replaced by zero at any time (also applicable to the lag phase, including the values prior to drug administration).

9.2.5. Pharmacokinetic parameters

Model-independent analysis will not include concentration data labeled NOS, NOR and NOA. BLQ and NOP values in the lag phase will be taken as zero. Lag phase is defined as the period between the zero of the time scale and the first time point with a concentration above the limit of quantification. Other BLQ/ NOP parameters will be ignored.

All possible attempts will be made to include all the concentration data in the analysis. If this is impossible, then it will be necessary to make a decision for each case separately – whether the parameter should be excluded from the half-life assessment or should enter the analysis.

If concentration is excluded only from the definition of half-lives, it will be used for all other counts (for example, descriptive statistics) and for a graphic image.

If the concentration value is excluded from all calculations, it will not be included in the graphical image or used for descriptive statistics calculations, as well as to determine the parameters. However, the excluded concentration will be included in the clinical study report tables with the appropriate note.

Descriptive statistics of a parameter is calculated only when the evaluation of at least 2/3 of the individual values of a particular parameter is available. If the current sampling time is not documented or will not be available for a specific time, the planned time will be used for the given timepoint. Pharmacokinetic parameters that cannot be determined will be labeled as "not calculated" (NC).

9.3. Safety Analysis

All deviations of the estimated safety parameters from normal values (including laboratory parameters) will be recorded as adverse events. Safety evaluation will be based on the incidence of adverse events and frequency of subjects with AE There will be summary tables with information on AEs and their description for each volunteer.

9.3.1. Adverse Events

Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 21.1) terminology. For evaluation, adverse events that occur prior to drug administration will be attributed to the screening period, and all other adverse events will be attributed to treatment periods.

Concomitant medications used to treat adverse events will be coded using WHO Drug Dictionary (Version, relevant at the time of encoding).

Adverse events evaluation will include different tables of frequency of events classified by severity of adverse events, evaluation of the association with the test drug/reference drug, relation to SAE and actions taken to the investigational product (including the need for premature study closure for these volunteers).

Descriptive statistics of laboratory findings over a long period of time will be provided to determine the difference from the baseline levels. A table of the frequency of changes will also be presented, taking into account the range of normal values between the baseline level and on-treatment last parameter.

9.3.2. Clinical Laboratory Evaluations

The results of the following laboratory research methods will be used as the analyzed safety parameters:

1) Complete blood count:

- Erythrocyte sedimentation rate (ESR)
- Hematocrit (Hct)
- Haemoglobin (Hb)
- Red blood cells/Erythrocytes
- Platelet count/Platelets
- White blood cells/Leukocytes

Automatic hematology analyzer

- Neutrophils (relative count)
- Eosinophils (relative count)
- Basophiles (relative count)
- Monocytes (relative content)
- Lymphocytes (relative content)

Manual count (if automatic hematology analyzer is not available)

- Neutrophils, stabs (Stabs)
- Neutrophils, polymorphonuclear (PMN)
- Eosinophils
- Basophils
- Monocytes

- Lymphocytes

2) Blood biochemistry:

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Glucose
- Creatinine
- Total bilirubin
- Total protein
- Total cholesterol
- Electrolytes: calcium, sodium and potassium

3) Urinalysis:

- Nitrites in urine
- Protein in urine
- Glucose in urine
- Ketones in urine
- Urobilinogen
- Bilirubin in urine
- RBC/Erythrocytes in urine
- WBC/Leukocytes in urine
- pH of urine

4) Urine sediment (microscopic examination):

- Bacteria in urine sediment
- Pavement epithelium in urine
- RBC/Erythrocytes in urine sediment
- WBC/Leukocytes in urine sediment

9.3.3. Vital Signs

The results of the following vital signs will be used as analyzed safety parameters:

- Blood pressure (systolic and diastolic)
- Pulse rate
- Body temperature
- Respiratory rate

9.3.4. Physical Examinations

The results of a physical examination for the following systems and organs will be evaluated as analyzed safety parameters:

- Skin, hair, nails
- Endocrine system
- Ears, nose, throat
- Cardiovascular system
- Gastrointestinal tract
- Nervous system
- Musculoskeletal system
- Reproductive system
- Urinary system

9.3.5. Electrocardiography

The following data obtained during the electrocardiographic study will be evaluated as the analyzed safety parameters:

- Heart rate
- PQ interval duration
- QRS interval duration
- QT interval duration

9.3.6. General assessment

The results of the overall evaluation will be evaluated as the analyzed safety parameters.

9.4. Restrictive laboratory tests

The results of the below laboratory test methods are not analyzed safety parameters, and are conducted only to confirm the compliance of the volunteer with the inclusion criteria and the absence of study exclusion/non-inclusion criteria.

Restrictive laboratory tests include:

1) Serological study of blood plasma for detection of infectious diseases:

- Hepatitis B surface antigen (qualitative test HbsAg)
- Anti-hepatitis C antibodies (qualitative total anti-HCV value)
- HIV-1 and HIV-2 (qualitative anti-HIV1/2)
- RPR test for syphilis (anticardiolipin test/microprecipitation test).

2) Pregnancy test (for females):

- Urine analysis for β-HCG

3) Urine drug screen for narcotic and potent substances:

- Marijuana
- Benzodiazepines
- Barbiturates
- Opiates
- Cocaine
- Amphetamines

4) Alcohol test:

- Breath alcohol test (using alcohol tester)

9.5. Other data

Individual volunteer data that is not significant for study endpoints, but necessary for recording the proper implementation of study procedures (method of administration data, time and date of investigational product administration, nutrition of subjects, visits) will be tabulated.

10. References

1. Decision of the Council of the Eurasian Economic Commission No. 85. On Approval of Good Pharmacovigilance Practice of the Eurasian Economic Union. Website eurasiancommission.org/ru/act/texnreg/deptexreg/LS1/Documents/32.pdf
2. et al. Determination of the relative bioavailability of 15 mg UH-AC 62 XX tablets compared with 15 mg UH-AC 62 XX capsules after oral administration over 7 days to healthy volunteers. Trial no. 107.74 Internal study report. 1992-07-06.
3. Methodical guidelines for bioequivalence studies. Ministry of Healthcare and Social Development of the Russian Federation, 2008. Website: rdg-cro.com/wp-content/uploads/2012/07/Guidelines-for-conducting-bioequivalence-studies-in-Russia.pdf
4. Sample size determination for bioequivalence assessment using a multiplicative model. Authors; Authors and affiliations.

Appendix 1.

Schedule of study procedures

Phase	Visit	Day (time interval)	Planned time after drug administration [h:min][1]	Time interval for blood sampling for PK [h:min]	Hospitalization	Randomization	Drug administration	Standard lab. tests[2]	Tests for exclusion	Blood sampling for PK	Physical examination	12-lead ECG	Vital signs[3]	Performance status	Adverse events	Food intake	Concomitant therapy
Screening[4]	1	-14 to -1						x	x[5]		x	x	x		x		x
Period I	2	-1	-16:00 to -10:00		x	x			x[6]		x	x[7]	x	x	x		x
		1	-2:00	-2:00 to 0:01						x			x		x		x
			0:00				x										
			0:30	±0:02						x							
			1:00	±0:02						x							
			2:00	±0:02						x							
			3:00	±0:05						x							
			4:00	±0:05						x						x	
			5:00	±0:05						x							
			6:00	±0:05						x			x		x	x	x
			7:00	±0:10						x							
			8:00	±0:10						x							
			9:00													x	
			10:00	±0:10						x							
			11:00													x	
			12:00	±0:10						x			x		x		x
		2	24:00	±0:15						x	x		x	x	x		x
			32:00	±0:15						x							
		3	48:00	±0:15						x	x		x	x	x		x
		4	72:00	±0:15				x		x	x		x	x	x		x

1. Time points for T/R drugs administration and for blood sampling for PK are strict.
2. Standard laboratory tests include clinical blood count, blood biochemistry and urinalysis.
   Clinical blood count: Erythrocyte sedimentation rate (ESR), Hematocrit (Hct), Haemoglobin (Hb), Erythrocytes/red blood cells (RBC), Platelet count, Leukocytes/White blood cells (WBC), Leukocyte formula (neutrophils, eosinophils, basophils, monocytes, lymphocytes). Perform test under fasting conditions.
   Blood biochemistry: Total protein, Glucose, Total cholesterol, Total bilirubin, Creatinine, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Electrolytes (Na, K, Ca). Perform test under fasting conditions.
   Urinalysis: pH, Protein, Glucose, Ketone bodies, Bilirubin, Urobilinogen, Erythrocytes, Nitrites, Leukocytes.
   Microscopic examination of urinary sediment: bacteria; Pavement epithelium; Erythrocytes; White blood cells.
   If ALT and/or AST values in blood biochemistry are ≥3 fold higher than ULN, together with total bilirubin ≥2 fold higher than ULN, the following laboratory tests should be repeated within 48-72 hours: ALT, AST and bilirubin (total and direct). If it is confirmed that ALT and/or AST values ≥3 fold higher than ULN together with total bilirubin ≥2 fold higher than ULN, complete blood count, serological tests and blood biochemistry should be performed and their findings should be provided to the Investigator and BI as soon as possible.
3. Vital signs (blood pressure (BP), pulse, body temperature, respiratory rate).
4. In addition to the procedures indicated in the study design, the following screening procedures are also performed: providing the volunteer with information about the study, signing an informed consent form, collecting demographic data, information on smoking and drinking alcohol, collecting medical history, taking concomitant medications, measuring body weight and height, the calculation of the body mass index (BMI).
5. At the screening visit the following tests for exclusion are performed: serological analysis of blood plasma for infection (qualitative analysis for HbsAg, qualitative analysis for total anti-HCV antibodies, qualitative analysis for antibodies to HIV1/2, test for syphilis); urine analysis for β-HCG (test strips for females); urine drug screen (test strips for the detection of marijuana, benzodiazepine, barbiturates, opiates, cocaine, amphetamines);breath alcohol test.
6. During the visit on Day -1, Period 1, the following analyzes for exclusion are performed to confirm that the patients meet study criteria: urine analysis for β-HCG (test strips for females); urine drug screen (test strips for the detection of marijuana, benzodiazepine, barbiturates, opiates, cocaine, amphetamines); breath alcohol test.
7. If the 12-lead ECG is performed on Day -7- -1 at screening, its results can be used on Day -1, Period I.

Phase	Visit	Day (time interval)	Planned time after drug administration [h:min][1]	Time interval for blood sampling for PK [h:min]	Hospitalization	Randomization	Drug administration	Standard lab. tests[2]	Tests for exclusion	Blood sampling for PK	Physical examination	12-lead ECG	Vital signs[3]	Performance status	Adverse events	Food intake	Concomitant therapy
Washout period[8]		7 days															
Period II	3	7	-16:00 to -10:00		x				x[9]		x	x	x	x	x		
		8	-2:00	-2:00 to 0:00						x	x		x		x		x
			0:00				x										
			0:30	±0:02						x							
			1:00	±0:02						x							
			2:00	±0:02						x							
			3:00	±0:05						x							
			4:00	±0:05						x						x	
			5:00	±0:05						x							
			6:00	±0:05						x			x	x	x	x	x
			7:00	±0:10						x							
			8:00	±0:10						x							
			9:00													x	
			10:00	±0:10						x							
			11:00													x	
			12:00	±0:10						x			x	x	x		x
		9	24:00	±0:15						x	x		x	x	x		x
			32:00	±0:15						x							
		10	48:00	±0:15						x	x		x	x	x		x
		11	72:00	±0:15				x		x	x	x	x	x	x		x
Follow-up	4	18							x[10]		x		x		x		x

8. Duration of washout period is calculated from the time of investigational product administration in the first study period to the time of the investigational product administration in the second study period. Interval between the hospital discharge of the volunteer in the first period and the hospitalization of the volunteer in the second study period is approximately 3.5 days.
9. During the visit on Day 7, Period 2, the following analyzes for exclusion are performed to confirm that the patients meet study criteria: urine analysis for β-HCG (test strips for females); urine drug screen (test strips for the detection of marijuana, benzodiazepine, barbiturates, opiates, cocaine, amphetamines); breath alcohol test.
10. Only urine analysis for β-HCG (test strips for females).

Appendix 2.

Table Templates

Accounting for volunteers

Table 1. Information on completion / early dropout from the study

Included in the study	
Safety population	
Pharmacokinetic population	
Completed according to the protocol	
Prematurely withdrawn (no further participation)	

Table 2. Disposition

Index	RT		TR		Total	
	N	%	N	%	N	%
First Period						
Treated Subjects						
Completed accordance to Protocol						
Early termination						
Protocol violation						
Withdrawal of consent						
Adverse event						
Lost to follow-up						
Other						
Second Period						
Treated Subjects						
Completed accordance to Protocol						
Early termination						
Protocol violation						
Withdrawal of consent						
Adverse event						
Lost to follow-up						
Other						

Initial characteristics of volunteers

Table 3. Descriptive statistics of demographic data

Index		RT		TR		Total	
		N	%	N	%	N	%
Sex	Male						
	Female						
Race	Caucasian						
	Other						

Table 4. Descriptive statistics of anthropometric data

Index	TR					
	N	SD	Mean	Median	Min	Max
Age						
Body weight						
Height						
BMI						
Index	**RT**					
	N	SD	Mean	Median	Min	Max
Age						
Body weight						
Height						
BMI						
Index	**Total**					
	N	SD	Mean	Median	Min	Max
Age						
Body weight						
Height						
BMI						

Safety indications - Adverse events

Table 5. Overall summary of Adverse events

Index	The Drug Test (T)		The Drug Reference (R)		Total	
	N	%	N	%	N	%
AE reported						
SAE reported						
Subjects with AE						
Subjects with SAE						
Is Life Threatening						
Persist or Significant Disability/Incapacity						
Requires or Prolongs Hospitalization						
Congenital Anomaly or Birth Defect						
Other Medically Important Serious Event						
Subjects with severe AEs						
Subjects with investigator defined drug−related AEs						
Subjects with AEs leading to discontinuation of trial drug						
Subjects with AEs of special interest						
Subjects with serious AEs						
Subjects with other significant AEs (according to ICH E3)						

Table 6. Frequency of subjects with adverse events by treatment, primary system organ class and preferred term.

System organ class/ Preferred term.	The Drug Test (T)			The Drug Reference (R)			Total	
	N	%		N	%		N	%
Total number of subjects								
Total with adverse events								
System organ class								
• Preferred term.								

Safety indicators - results of instrumental methods

Table 7. Dynamics of ECG indices during the study (Screening - Second Period)

Index	Relative time	The Drug Test (T)							The Drug Reference (R)							Total					
		N	SD	Mean	Median	Min	Max		N	SD	Mean	Median	Min	Max		N	SD	Mean	Median	Min	Max
Heart Rate	Screening Visit																				
	First Period Admission (Day -1)																				
	Second Period Admission (Day 7)																				
	Second Period (Day 11)																				
PQ	Screening Visit																				
	First Period Admission (Day -1)																				
	Second Period Admission (Day 7)																				
	Second Period (Day 11)																				
QRS	Screening Visit																				
	First Period Admission (Day -1)																				
	Second Period Admission (Day 7)																				
	Second Period (Day 11)																				
QT	Screening Visit																				
	First Period Admission (Day -1)																				
	Second Period Admission (Day 7)																				
	Second Period (Day 11)																				

Table 8. Assessment of ECG indices during the study (Screening - Second Period).

Index	Relative time	The Drug Test (T)					The Drug Reference (R)					Total			
		Normal		Abnormal			Normal		Abnormal			Normal		Abnormal	
		N	%	N	N		N	N	%	N		%	N	%	N
Heart Rate	Screening Visit														
	First Period Admission (Day -1)														
	Second Period Admission (Day 7)														
	Second Period (Day 11)														
PQ	Screening Visit														
	First Period Admission (Day -1)														
	Second Period Admission (Day 7)														
	Second Period (Day 11)														
QRS	Screening Visit														
	First Period Admission (Day -1)														
	Second Period Admission (Day 7)														
	Second Period (Day 11)														
QT	Screening Visit														
	First Period Admission (Day -1)														
	Second Period Admission (Day 7)														
	Second Period (Day 11)														

Table 9. Dynamics of vital signs during the study (Screening - Period 1 - Period 2 - Visit of follow-up observation)

Index	Visit/Relative time	The Drug Test (T)							The Drug Reference (R)							Total					
		N	SD	Mean	Median	Min	Max		N	SD	Mean	Median	Min	Max		N	SD	Mean	Median	Min	Max
Pulse rate	Screening Visit																				
	First Period Admission (Day -1)																				
	Day 1 (-2:00)																				
	Day 1 (6:00)																				
	Day 1 (12:00)																				
	Day 2 (24:00)																				
	Day 3 (48:00)																				
	Day 4 (72:00)																				
	Second Period Admission (Day 7)																				
	Day 8 (-2:00)																				
	Day 8 (6:00)																				
	Day 8 (12:00)																				
	Day 9 (24:00)																				
	Day 10 (48:00)																				
	Day 11 (72:00)																				
	Follow-Up Visit (Day 18)																				
Systolic blood pressure	Screening Visit																				
	First Period Admission (Day -1)																				
	Day 1 (-2:00)																				
	Day 1 (6:00)																				
	Day 1 (12:00)																				
	Day 2 (24:00)																				
	Day 3 (48:00)																				
	Day 4 (72:00)																				
	Second Period Admission (Day 7)																				
	Day 8 (-2:00)																				
	Day 8 (6:00)																				
	Day 8 (12:00)																				
	Day 9 (24:00)																				
	Day 10 (48:00)																				
	Day 11 (72:00)																				
	Follow-Up Visit (Day 18)																				

Diastolic blood pressure	Screening Visit																				
	First Period Admission (Day -1)																				
	Day 1 (-2:00)																				
	Day 1 (6:00)																				
	Day 1 (12:00)																				
	Day 2 (24:00)																				
	Day 3 (48:00)																				
	Day 4 (72:00)																				
	Second Period Admission (Day 7)																				
	Day 8 (-2:00)																				
	Day 8 (6:00)																				
	Day 8 (12:00)																				
	Day 9 (24:00)																				
	Day 10 (48:00)																				
	Day 11 (72:00)																				
	Follow-Up Visit (Day 18)																				
Body temperature	Screening Visit																				
	First Period Admission (Day -1)																				
	Day 1 (-2:00)																				
	Day 1 (6:00)																				
	Day 1 (12:00)																				
	Day 2 (24:00)																				
	Day 3 (48:00)																				
	Day 4 (72:00)																				
	Second Period Admission (Day 7)																				
	Day 8 (-2:00)																				
	Day 8 (6:00)																				
	Day 8 (12:00)																				
	Day 9 (24:00)																				
	Day 10 (48:00)																				
	Day 11 (72:00)																				
	Follow-Up Visit (Day 18)																				
Respiratory rate	Screening Visit																				
	First Period Admission (Day -1)																				
	Day 1 (-2:00)																				
	Day 1 (6:00)																				
	Day 1 (12:00)																				
	Day 2 (24:00)																				

	Day 3 (48:00)																				
	Day 4 (72:00)																				
	Second Period Admission (Day 7)																				
	Day 8 (-2:00)																				
	Day 8 (6:00)																				
	Day 8 (12:00)																				
	Day 9 (24:00)																				
	Day 10 (48:00)																				
	Day 11 (72:00)																				
	Follow-Up Visit (Day 18)																				

Table 10. Assessment of vital signs during the study (Screening - Period 1 - Period 2 - Visit of follow-up observation)

Index	Visit/Relative time	The Drug Test (T)					The Drug Reference (R)					Total			
		Normal		Abnormal			Normal		Abnormal			Normal		Abnormal	
		N	%	N	N		N	%	N	%		N	%	N	%
Pulse rate	Screening Visit														
	First Period Admission (Day -1)														
	Day 1 (-2:00)														
	Day 1 (6:00)														
	Day 1 (12:00)														
	Day 2 (24:00)														
	Day 3 (48:00)														
	Day 4 (72:00)														
	Second Period Admission (Day 7)														
	Day 8 (-2:00)														
	Day 8 (6:00)														
	Day 8 (12:00)														
	Day 9 (24:00)														
	Day 10 (48:00)														
	Day 11 (72:00)														
	Follow-Up Visit (Day 18)														
Systolic blood pressure	Screening Visit														
	First Period Admission (Day -1)														
	Day 1 (-2:00)														
	Day 1 (6:00)														
	Day 1 (12:00)														
	Day 2 (24:00)														
	Day 3 (48:00)														
	Day 4 (72:00)														
	Second Period Admission (Day 7)														
	Day 8 (-2:00)														
	Day 8 (6:00)														
	Day 8 (12:00)														
	Day 9 (24:00)														
	Day 10 (48:00)														
	Day 11 (72:00)														
	Follow-Up Visit (Day 18)														
1 0	Screening Visit														

	First Period Admission (Day -1)														
	Day 1 (-2:00)														
	Day 1 (6:00)														
	Day 1 (12:00)														
	Day 2 (24:00)														
	Day 3 (48:00)														
	Day 4 (72:00)														
	Second Period Admission (Day 7)														
	Day 8 (-2:00)														
	Day 8 (6:00)														
	Day 8 (12:00)														
	Day 9 (24:00)														
	Day 10 (48:00)														
	Day 11 (72:00)														
	Follow-Up Visit (Day 18)														
Body temperature	Screening Visit														
	First Period Admission (Day -1)														
	Day 1 (-2:00)														
	Day 1 (6:00)														
	Day 1 (12:00)														
	Day 2 (24:00)														
	Day 3 (48:00)														
	Day 4 (72:00)														
	Second Period Admission (Day 7)														
	Day 8 (-2:00)														
	Day 8 (6:00)														
	Day 8 (12:00)														
	Day 9 (24:00)														
	Day 10 (48:00)														
	Day 11 (72:00)														
	Follow-Up Visit (Day 18)														
Respiratory rate	Screening Visit (Day 18)														
	First Period Admission (Day -1)														
	Day 1 (-2:00)														
	Day 1 (6:00)														
	Day 1 (12:00)														
	Day 2 (24:00)														
	Day 3 (48:00)														

	Day 4 (72:00)														
	Second Period Admission (Day 7)														
	Day 8 (-2:00)														
	Day 8 (6:00)														
	Day 8 (12:00)														
	Day 9 (24:00)														
	Day 10 (48:00)														
	Day 11 (72:00)														
	Follow-Up Visit (Day 18)														

Table 11. Assessment of Physical examination by time (Screening- Follow

Relative time	Body system and site	The Drug Test (T)				The Drug Reference (R)				Total			
		Normal		Abnormal		Normal		Abnormal		Normal		Abnormal	
		N	%	N	%	N	%	N	%	N	%	N	%
Screening													
Day -14 to -1	Skin, hair, nails												
	Endocrine system												
	Ear, nose, throat												
	Cardiovascular system												
	Gastrointestinal system												
	Nervous system												
	Musculoskeletal system												
	Reproductive system												
	Renal system												
First Period													
Day -1, -10:00 - -16:00	Skin, hair, nails												
	Endocrine system												
	Ear, nose, throat												
	Cardiovascular system												
	Gastrointestinal system												
	Nervous system												
	Musculoskeletal system												
	Reproductive system												
	Renal system												
Day 2, + 24:00	Skin, hair, nails												
	Endocrine system												
	Ear, nose, throat												
	Cardiovascular system												
	Gastrointestinal system												
	Nervous system												
	Musculoskeletal system												
	Reproductive system												
	Renal system												
Day 3, + 48:00	Skin, hair, nails												
	Endocrine system												
	Ear, nose, throat												
	Cardiovascular system												
	Gastrointestinal system												
	Nervous system												
	Musculoskeletal system												

	Reproductive system													
	Renal system													
Day 4, + 72:00	Skin, hair, nails													
	Endocrine system													
	Ear, nose, throat													
	Cardiovascular system													
	Gastrointestinal system													
	Nervous system													
	Musculoskeletal system													
	Reproductive system													
	Renal system													
Second Period														
-10:00 - -16:00	Skin, hair, nails													
	Endocrine system													
	Ear, nose, throat													
	Cardiovascular system													
	Gastrointestinal system													
	Nervous system													
	Musculoskeletal system													
	Reproductive system													
	Renal system													
+ 24:00	Skin, hair, nails													
	Endocrine system													
	Ear, nose, throat													
	Cardiovascular system													
	Gastrointestinal system													
	Nervous system													
	Musculoskeletal system													
	Reproductive system													
	Renal system													
+ 48:00	Skin, hair, nails													
	Endocrine system													
	Ear, nose, throat													
	Cardiovascular system													
	Gastrointestinal system													
	Nervous system													
	Musculoskeletal system													
	Reproductive system													
	Renal system													

+ 72:00	Skin, hair, nails														
	Endocrine system														
	Ear, nose, throat														
	Cardiovascular system														
	Gastrointestinal system														
	Nervous system														
	Musculoskeletal system														
	Reproductive system														
	Renal system														
Follow up															
Not applicable	Skin, hair, nails														
	Endocrine system														
	Ear, nose, throat														
	Cardiovascular system														
	Gastrointestinal system														
	Nervous system														
	Musculoskeletal system														
	Reproductive system														
	Renal system														
First and Second Period															
-10:00 - -16:00	Skin, hair, nails														
	Endocrine system														
	Ear, nose, throat														
	Cardiovascular system														
	Gastrointestinal system														
	Nervous system														
	Musculoskeletal system														
	Reproductive system														
	Renal system														
+ 24:00	Skin, hair, nails														
	Endocrine system														
	Ear, nose, throat														
	Cardiovascular system														
	Gastrointestinal system														
	Nervous system														
	Musculoskeletal system														
	Reproductive system														
	Renal system														
4 8 .. 0	Skin, hair, nails														

	Endocrine system									
	Ear, nose, throat									
	Cardiovascular system									
	Gastrointestinal system									
	Nervous system									
	Musculoskeletal system									
	Reproductive system									
	Renal system									
+ 72:00	Skin, hair, nails									
	Endocrine system									
	Ear, nose, throat									
	Cardiovascular system									
	Gastrointestinal system									
	Nervous system									
	Musculoskeletal system									
	Reproductive system									
	Renal system									

Safety indicators - laboratory results

Table 12 Dynamics of biochemical blood test parameters during the study (Screening-Second period)

Visit	Index	The Drug Test (T)						The Drug Reference (R)						Total					
		N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max
Screening	Total protein (g/l)																		
	Alkaline phosphatase (U/l)																		
	ALT (U/l)																		
	AST (U/l)																		
	Glucose (Mmol/l)																		
	Total cholesterol (Mmol/l)																		
	Total bilirubin (Mcmol/l)																		
	Creatinine (Mcmol/l)																		
	Potassium (Mmol/l)																		
	Sodium (Mmol/l)																		
	Calcium (Mmol/l)																		
First Period (72:00)	Total protein (g/l)																		
	Alkaline phosphatase (U/l)																		
	ALT (U/l)																		
	AST (U/l)																		
	Glucose (Mmol/l)																		
	Total cholesterol (Mmol/l)																		
	Total bilirubin (Mcmol/l)																		
	Creatinine (Mcmol/l)																		
	Potassium (Mmol/l)																		
	Sodium (Mmol/l)																		
	Calcium (Mmol/l)																		
Second Period (72:00)	Total protein (g/l)																		
	Alkaline phosphatase (U/l)																		
	ALT (U/l)																		
	AST (U/l)																		
	Glucose (Mmol/l)																		
	Total cholesterol (Mmol/l)																		
	Total bilirubin (Mcmol/l)																		
	Creatinine (Mcmol/l)																		
	Potassium (Mmol/l)																		
	Sodium (Mmol/l)																		
	Calcium (Mmol/l)																		

First and Second Periods (72:00)	Total protein (g/l)													
	Alkaline phosphatase (U/l)													
	ALT (U/l)													
	AST (U/l)													
	Glucose (Mmol/l)													
	Total cholesterol (Mmol/l)													
	Total bilirubin (Mcmol/l)													
	Creatinine (Mcmol/l)													
	Potassium (Mmol/l)													
	Sodium (Mmol/l)													
	Calcium (Mmol/l)													

Table 13. Assessment of biochemical blood test parameters during the study (Screening-Second period)

Visit	Index	The Drug Test (T)				The Drug Reference (R)				Total			
		Normal		Abnormal		Normal		Abnormal		Normal		Abnormal	
		N	%	N	N	N	%	N	%	N	%	N	%
Screening	Total protein (g/l)												
	Alkaline phosphatase (U/l)												
	ALT (U/l)												
	AST (U/l)												
	Glucose (Mmol/l)												
	Total cholesterol (Mmol/l)												
	Total bilirubin (Mcmol/l)												
	Creatinine (Mcmol/l)												
	Potassium (Mmol/l)												
	Sodium (Mmol/l)												
	Calcium (Mmol/l)												
First Period (72:00)	Total protein (g/l)												
	Alkaline phosphatase (U/l)												
	ALT (U/l)												
	AST (U/l)												
	Glucose (Mmol/l)												
	Total cholesterol (Mmol/l)												
	Total bilirubin (Mcmol/l)												
	Creatinine (Mcmol/l)												
	Potassium (Mmol/l)												
	Sodium (Mmol/l)												
	Calcium (Mmol/l)												
Second Period (72:00)	Total protein (g/l)												
	Alkaline phosphatase (U/l)												
	ALT (U/l)												
	AST (U/l)												
	Glucose (Mmol/l)												
	Total cholesterol (Mmol/l)												
	Total bilirubin (Mcmol/l)												
	Creatinine (Mcmol/l)												
	Potassium (Mmol/l)												
	Sodium (Mmol/l)												
	Calcium (Mmol/l)												
P	Total protein (g/l)												

Visit	Index	The Drug Test (T)					The Drug Reference (R)					Total			
		Normal		Abnormal			Normal		Abnormal			Normal		Abnormal	
		N	%	N	N		N	%	N	%		N	%	N	%
	Alkaline phosphatase (U/l)														
	ALT (U/l)														
	AST (U/l)														
	Glucose (Mmol/l)														
	Total cholesterol (Mmol/l)														
	Total bilirubin (Mcmol/l)														
	Creatinine (Mcmol/l)														
	Potassium (Mmol/l)														
	Sodium (Mmol/l)														
	Calcium (Mmol/l)														

Table 14 Dynamics of the parameters of the general blood test during the study (Screening- Second Period)

Visit	Index	The Drug Test (T)						The Drug Reference (R)						Total					
		N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max
Screening	Red blood cells (x10^{12}/l)																		
	White blood cells (x10^{9}/l)																		
	Neutrophils (%)																		
	Eosinophils (%)																		
	Basophils (%)																		
	Monocytes (%)																		
	Lymphocytes (%)																		
	Hematocrit (%)																		
	Hemoglobin (g/l)																		
	Platelet count (x10^{9}/l)																		
	ESR (mm/h)																		
First Period (72:00)	Red blood cells (x10^{12}/l)																		
	White blood cells (x10^{9}/l)																		
	Neutrophils (%)																		
	Eosinophils (%)																		
	Basophils (%)																		
	Monocytes (%)																		
	Lymphocytes (%)																		
	Hematocrit (%)																		
	Hemoglobin (g/l)																		
	Platelet count (x10^{9}/l)																		
	ESR (mm/h)																		
Second Period (72:00)	Red blood cells (x10^{12}/l)																		
	White blood cells (x10^{9}/l)																		
	Neutrophils (%)																		
	Eosinophils (%)																		
	Basophils (%)																		
	Monocytes (%)																		
	Lymphocytes (%)																		
	Hematocrit (%)																		
	Hemoglobin (g/l)																		
	Platelet count (x10^{9}/l)																		
	ESR (mm/h)																		
P d n	Red blood cells (x10^{12}/l)																		

Visit	Index	The Drug Test (T)						The Drug Reference (R)						Total					
		N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max
	White blood cells (x10^9/l)																		
	Neutrophils (%)																		
	Eosinophils (%)																		
	Basophils (%)																		
	Monocytes (%)																		
	Lymphocytes (%)																		
	Hematocrit (%)																		
	Hemoglobin (g/l)																		
	Platelet count (x10^9/l)																		
	ESR (mm/h)																		

Table 15. Assessment of the parameters of the general blood test during the study (Screening- Second Period)

Visit	Index	The Drug Test (T)				The Drug Reference (R)				Total			
		Normal		Abnormal		Normal		Abnormal		Normal		Abnormal	
		N	%	N	N	N	%	N	%	N	%	N	%
Screening	Red blood cells (x10^{12}/l)												
	White blood cells (x10^{9}/l)												
	Neutrophils (%)												
	Eosinophils (%)												
	Basophils (%)												
	Monocytes (%)												
	Lymphocytes (%)												
	Hematocrit (%)												
	Hemoglobin (g/l)												
	Platelet count (x10^{9}/l)												
	ESR (mm/h)												
First Period (72:00)	Red blood cells (x10^{12}/l)												
	White blood cells (x10^{9}/l)												
	Neutrophils (%)												
	Eosinophils (%)												
	Basophils (%)												
	Monocytes (%)												
	Lymphocytes (%)												
	Hematocrit (%)												
	Hemoglobin (g/l)												
	Platelet count (x10^{9}/l)												
	ESR (mm/h)												
Second Period (72:00)	Red blood cells (x10^{12}/l)												
	White blood cells (x10^{9}/l)												
	Neutrophils (%)												
	Eosinophils (%)												
	Basophils (%)												
	Monocytes (%)												
	Lymphocytes (%)												
	Hematocrit (%)												
	Hemoglobin (g/l)												
	Platelet count (x10^{9}/l)												
	ESR (mm/h)												
co nd Pe rio	Red blood cells (x10^{12}/l)												
	White blood cells (x10^{9}/l)												

Visit	Index	The Drug Test (T)				The Drug Reference (R)				Total			
		Normal		Abnormal		Normal		Abnormal		Normal		Abnormal	
		N	%	N	N	N	%	N	%	N	%	N	%
	Neutrophils (%)												
	Eosinophils (%)												
	Basophils (%)												
	Monocytes (%)												
	Lymphocytes (%)												
	Hematocrit (%)												
	Hemoglobin (g/l)												
	Platelet count ($x10^9$/l)												
	ESR (mm/h)												

Table 16. Evaluation of the results of the general analysis of urine (norm, pathology) (Screening- Second Period).

Visit	Index	The Drug Test (T)				The Drug Reference (R)				Total			
		Normal		Abnormal		Normal		Abnormal		Normal		Abnormal	
		N	%	N	%	N	%	N	%	N	%	N	%
Screening	pH												
	Protein (g/l)												
	Urobilinogen (Mcmol/l)												
	Glucose (Negative/Positive)												
	Ketones (Negative/Positive)												
	Bilirubin (Negative/Positive)												
	Nitrites (Negative/Positive)												
	Red blood cells (in a field of view)												
	White blood cells (in a field of view)												
First Period (72:00)	pH												
	Protein (g/l)												
	Urobilinogen (Mcmol/l)												
	Glucose (Negative/Positive)												
	Ketones (Negative/Positive)												
	Bilirubin (Negative/Positive)												
	Nitrites (Negative/Positive)												
	Red blood cells (in a field of view)												
	White blood cells (in a field of view)												
Second Period (72:00)	pH												
	Protein (g/l)												
	Urobilinogen (Mcmol/l)												
	Glucose (Negative/Positive)												
	Ketones (Negative/Positive)												
	Bilirubin (Negative/Positive)												
	Nitrites (Negative/Positive)												
	Red blood cells (in a field of view)												
	White blood cells (in a field of view)												
First and Second Periods (72:00)	pH												
	Protein (g/l)												
	Urobilinogen (Mcmol/l)												
	Glucose (Negative/Positive)												
	Ketones (Negative/Positive)												
	Bilirubin (Negative/Positive)												
	Nitrites (Negative/Positive)												
	Red blood cells (in a field of view)												
	White blood cells (in a field of view)												

Table 17. Dynamics of the microscopy of urinary sediment (Screening- Second Period)

Visit	Index	The Drug Test (T)						The Drug Reference (R)						Total					
		N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max	N	SD	Mean	Median	Min	Max
Screening	Red blood cells (in a field of view)																		
	White blood cells (in a field of view)																		
	Epith Cells (in a field of view)																		
	Bacteria (in a field of view)																		
First Period (72:00)	Red blood cells (in a field of view)																		
	White blood cells (in a field of view)																		
	Epith Cells (in a field of view)																		
	Bacteria (in a field of view)																		
Second Period (72:00)	Red blood cells (in a field of view)																		
	White blood cells (in a field of view)																		
	Epith Cells (in a field of view)																		
	Bacteria (in a field of view)																		
First and Second Periods (72:00)	Red blood cells (in a field of view)																		
	White blood cells (in a field of view)																		
	Epith Cells (in a field of view)																		
	Bacteria (in a field of view)																		

Table 18. Evaluation of the results of microscopy of urinary sediment (Screening- Second Period)

Visit	Index	The Drug Test (T)					The Drug Reference (R)					Total			
		Normal		Abnormal			Normal		Abnormal			Normal		Abnormal	
		N	%	N	%		N	%	N	%		N	%	N	%
Screening	Red blood cells (in a field of view)														
	White blood cells (in a field of view)														
	Epith Cells (in a field of view)														
	Bacteria (in a field of view)														
First Period (72:00)	Red blood cells (in a field of view)														
	White blood cells (in a field of view)														
	Epith Cells (in a field of view)														
	Bacteria (in a field of view)														
Second Period (72:00)	Red blood cells (in a field of view)														
	White blood cells (in a field of view)														
	Epith Cells (in a field of view)														
	Bacteria (in a field of view)														
First and Second Periods (72:00)	Red blood cells (in a field of view)														
	White blood cells (in a field of view)														
	Epith Cells (in a field of view)														
	Bacteria (in a field of view)														

Table 19. Bioequivalence evaluation using Least Square Means by Formulation ratios and their 90% confidence intervals after single oral administration of Movalis® capsules 15 mg (T) and Movalis® tablets 15 mg (R) under fasting state

PK parameter	N_T	N_R	$GeoLSM_T$	$GeoLSM_R$	GeoLSM T/R ratio, %	90% Confidence interval, %		CV_{intra}, %	Power, %
AUC_{0-t}									
C_{max}									
$AUC_{0-\infty}$									

Table 20. Main statistics (Number of observations, Geometric means and GeoCVs) of PK parameters by formulation and Geometric Means (T/R) ratios after single oral administration of Movalis® capsules 15 mg (T) and Movalis® tablets 15 mg (R) under fasting state

PK parameter	The Drug Test (T)			The Drug Reference (R)			Geo Means T/R Ratio (%)
	N	Geo Mean	Geo CV (%)	N	GeoMean	Geo CV (%)	
AUC_{0-t} (ng·h/ml)							
$AUC_{0-\infty}$ (ng·h/ml)							
C_{max} (ng/ml)							

Appendix 3.

List of the study datasets

Name of form	Code of form	Screening	First period, admission	First period	Second period, admission	Second period	Follow-up visit	Unschedul- ed visit	Main forms	Screenfailure data
Inclusion	F_ENRL	X	-	-	-	-	-	-	-	-
Demographic information	F_DMGR	X	-	-	-	-	-	-	-	X
Bad habits	F_BADHB	X	-	-	-	-	-	-	-	X
Past and concomitant deseases (repeat form)	F_DIS	X	-	-	-	-	-	-	-	X
Pharmacological history over last 3 months (repeat form)	F_MHIST	X	-	-	-	-	-	-	-	X
Allergic history	F_ALERG	X	-	-	-	-	-	-	-	X
Physical examination	F_PHIS	X	X	-	X	-	X	X	-	X
Anthropometric parameters	F_ANTHR	X	-	-	-	-	-	-	-	X
Vital signs	F_MAIN	X	X		X		X	X	-	X
Electrocardiography	F_ECG	X	X		X	X	-	X	-	X
Complete blood count	F_BLOOD	X	-	X	-	X	-	X	-	X
Blood serum chemistry	F_BBLOOD	X	-	X	-	X	-	X	-	X
Serology	F_SERO	X	-	-	-	-	-	-	-	X
Urinalysis	F_URINA	X	-	X	-	X	-	X	-	X
Microscopic examination of urine sediment	F_MICRO	X	-	X	-	X	-	X	-	X
Pregnancy test	F_TEST	X	X	-	X	-	X	-	-	X
Urine drug screen	F_DRUG	X	X	-	X	-	-	-	-	X
Alcohol breath test	F_ALCO	X	X	-	X	-	-	-	-	X
Inclusion criteria	F_CRIT	X	-	-	-	-	-	-	-	X
Visit comments	F_COMM	X	X	X	X	X	X	X	-	X
Visit information	F_INFO		X	X	X	X	X	X	-	-
Randomization	F_RAND	-	X	-	-	-	-	-	-	-
Global assessment	F_GLOB	-	X	-	X	-	-	X	-	-
Physical examination (repeat form)	F_PHIST	-	-	X	-	X	-	-	-	-
Vital signs (repeat form)	F_MAINT	-	-	X	-	X	-	-	-	-
AE/SAE evaluation and cncomitant therapy (repeat form)	F_AE_TH	-	-	X	-	X	-	-	-	-
Global assessment (repeat form)	F_GLOBT	-	-	X	-	X	-	-	-	-
Administration of the study drug	F_DRUGT	-	-	X	-	X	-	-	-	-
Collection of PK blood samples (repeat form)	F_FARM	-	-	X	-	X	-	-	-	-

Name of form	Code of form	Screening	First period, admission	First period	Second period, admission	Second period	Follow-up visit	Unschedul- ed visit	Main forms	Screenfailure data
Meals	F_EAT	-	-	**X**	-	**X**	-	-	-	-
End of participation	F_END	-	-	-	-	-	-	-	**X**	-
Adverse event Form (repeat form)	F_AE	-	-	-	-	-	-	-	**X**	-
Concomitant therapy (repeat form)	F_TREAT	-	-	-	-	-	-	-	**X**	-
Main screen failure information	F_SF	-	-	-	-	-	-	-		**X**