Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		Synopsis	Boehringer Ingelheim
BI proprietary name: Movalis®			
BI investigational product: Meloxicam (UHAC 62 XX)		**Page:** 1 of 5	
Report date: 2019	**Trial no./Doc. no.:** 0107-0277/ c26468095-01	**Dates of trial:** From 09 Oct 2018 to 06 Nov 2018	**Date of revision:** Not applicable

Title of trial

An open-label, randomised, single-dose, two-way crossover study in healthy male and female subjects 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.

Lay title

A study to compare the amount of meloxicam in the blood when it is taken as capsules or as tablets.

Principal/Coordinating investigator

Dr. [redacted]. MD, PhD.

[redacted] Russia.

Trial sites with screened subjects

40 subjects were screened and of which, 26 subjects were randomized and treated at one site in Russian Federation.

Publications

Not applicable

Clinical phase: Phase I- Bioequivalence trial

Objectives

Primary objective:

To investigate the relative bioavailability of Movalis® capsules 15 mg versus Movalis® tablets 15 mg.

Secondary objective

To determine the bioequivalence between Movalis® capsules 15 mg and Movalis® tablets 15 mg

To assess the safety and the tolerability of Movalis® capsules 15 mg and Movalis® tablets 15 mg.

Methodology

The trial was a randomised, two-period, two-sequence, single-dose, open-label and crossover trial in healthy male and female subjects in fasting conditions.

Hospitalization of subjects occurred from the evening before administration until 24 hours postadministration.

Product administration: one dose of Movalis® capsules 15 mg (Test product) or Movalis® tablets 15 mg (Reference product) in fasting conditions, in each trial period.

Blood samplings were collected before administration (t = -2:00 h) and at the following times after each administration: 0:30,1:00, 2:00,3:00, 4:00, 5:00, 6:00, 7:00, 8:00, 10:00, 12:00, 24:00, 32:00. 48:00 and 72:00 h

Washout period: 7 days between drug administrations.

Analytical method: HPLC-MS/MS

Relevant pharmacokinetic parameters: AUC_{0-t} , C_{max} and $AUC_{0-\infty}$.

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Number of subjects

Planned: Screened: 40 subjects.
Entered: 26 subjects.

Actual: Screened: 40 subjects.

Entered: 26 subjects.

Movalis® capsules 15 mg (Test formulation , T)

Entered: 26 Treated: 26 Analyzed (for primary endpoint): 26

Movalis® tablets 15 mg (Reference formulation, R)

Entered: 26 Treated: 26 Analyzed (for primary endpoint): 26

Diagnosis

Not applicable

Main criteria for inclusion

The trial included healthy male and female subjects aged 18-45 years, with body mass index by Quetelet between 18.50 -29.99 kg/m^2, inclusive.

The verified diagnosis was "healthy" according to the conclusion of the investigator, based on the information in the anamnesis, the results of the physical examination, the ECG, the results of measurement of vital signs (blood pressure, heart rate, breathing rate, and body temperature), and laboratory indicators.

BI investigational product:	Movalis® capsules (T)
Dose:	15 mg
Mode of administration:	Oral with 200 mL of water after an overnight fast of at least 10 h
Expiry date:	30.06.2020.
Manufacturing Batch No.:	744608A

Comparator product:	Movalis® tablets (R)
Dose:	15 mg
Expiry date:	28.02.2021.
Manufacturing Batch No.:	844072
Mode of administration:	Oral with 200 mL of water after an overnight fast of at least 10 h

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Duration of treatment

One day (single dose) for each period

clinical pharmacology criteria for evaluation

Primary endpoints: AUC_{0-t} and $C_{max.}$

Secondary endpoints: $AUC_{0-\infty}$.

Further endpoints: AUC_{res}, K_{el}, t_{max} and t½.

Safety criteria for evaluation

Vital signs (blood pressure, pulse rate, temperature, respiratory rate), global assessment, physical examination, 12-lead ECG, laboratory tests, adverse events.

Statistical methods

To demonstrate bioequivalence, the 90% confidence interval for AUC_{0-t} and C_{max} ratios of the Test and Reference formulations must be comprised within the acceptance interval of 80.00–125.00%.

Bioequivalence criteria are:

- the limits of the estimated confidence interval for AUC_{0-t} were within 80.00–125.00%;
- the limits of the estimated confidence interval for C_{max} were within 80.00–125.00%:

Following logarithmic transformation of AUC_{0-t} and C_{max}, the values were subjected to analysis of variance (ANOVA) in a pre-specified model in TSAP including following factors: sequence, subjects within sequence, period, and formulation. The factor 'subjects grouped within sequence' was evaluated as a random effect, meanwhile the other factors were evaluated as fixed effects. An additional analysis of variance was performed according to the model with fixed factors "sequence", "subjects within sequence", "period" and "formulation" as indicated in the Decision of the Eurasian Economic Commission No. 85.

For the evaluation of the bioequivalence, the point estimates and the 90%-confidence intervals (CI) for the comparison between Test and Reference formulations were calculated for the pharmacokinetic parameters AUC_{0-t} and C_{max} using the residual mean square error from the multifactorial ANOVA. This approach is equivalent to two one-sided tests of the null hypothesis about the non-bioequivalence at a 5% significance level for each test. In addition to this, the point estimates and the 90%-confidence intervals (CI) for secondary endpoint $AUC_{0-\infty}$ was also calculated.

For this purpose, the corresponding data were preliminary log-transformed, the ANOVA was carried out and point estimators and confidence intervals were established (in the log scale). Then the obtained point estimates and confidence intervals were back-transformed to the original scale to be expressed in nonlog geometric means.

Descriptive statistics of all pharmacokinetic parameters included arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation.

Descriptive statistics of all safety parameters included arithmetic mean, standard deviation, minimum, median, maximum

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No interim analysis was planned or performed.

SUMMARY – CONCLUSIONS

Trial subjects and compliance with the clinical trial protocol

A total of 40 subjects were screened in the trial. Of these, 26 subjects were randomized and treated with the trial medications.

The overall mean (±SD) age was 30.0 (±6.6) years. The trial included 21 women (80.8%) and 5 men (19.2%). All subjects were Caucasians.

Compliance:

All trial procedures were performed under strict control of the clinical site staff, which ensured full compliance of subjects with the requirements of the trial protocol.

No important protocol deviations were reported.

Clinical pharmacology results

The geometric mean ratio, the limits thereof and the intraindividual CV of the pharmacokinetic parameters of the exposure (AUC_{0-t} and $AUC_{0-\infty}$) and the peak concentration (C_{max}) of meloxicam, after administration of Test and Reference products were calculated as follows:

PK parameter	Number of subjects in R	Number of subjects in T	Geometric mean (T)	Standard error for T (gSE T)	Geometric mean (R)	Standard error for R (gSE R)	Geometric mean ratio T/R, %	Lower limit of 90% CI	Upper limit of 90% CI	CV_{intra}
AUC_{0-t}	26	26	27870.56	1.06	30051.25	1.06	92.74	89.02	96.62	8.66
C_{max}	26	26	1131.12	1.04	1432.83	1.04	78.94	73.70	84.56	14.57
$AUC_{0-\infty}$	26	26	32863.87	1.09	33867.43	1.09	97.04	92.57	101.72	9.96

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Safety results

During the trial, all abnormalities in laboratory examination were reported as AE. A total of 7 AEs were reported in 3 subjects.

- 6 adverse events were reported after the Test drug intake. Of those, 4AEs were assessed as related to the Test drug by the investigator
- One adverse event was reported after the Reference Drug intake. It was assessed as not related to the Reference Drug by the investigator

All adverse events were categorised as mild adverse events. No serious adverse events or adverse events of special interest were reported. All subjects completely recovered before the end of the trial, without the use of concomitant therapy or other treatment methods.

No death was reported in the trial.

Conclusions

The statistical analysis of the pharmacokinetic data demonstrates that the point estimate and the 90% confidence interval of geometric mean ratio for AUC_{0-t} (Test vs. Reference) are within the acceptance interval of 80.00–125.00%, whereas point estimate and the 90%-confidence interval of geometric mean ratio of C_{max} (Test vs. Reference) are not within the acceptance interval of 80.00–125.00%. Therefore, the Test formulation (Movalis® capsules 15 mg) and the Reference formulation (Movalis® tablets 15 mg) are not bioequivalent in this study.