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**.

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| **Name of company:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Not applicable | | **EudraCT No.:** 2010-023059-27 | |
| **Name of active ingredient:** BI 10773 | | **Page:** 1 of 5 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 15 JUL 2011 | **Trial No. / U No.:** 1245.43 / U11-1964-01 | **Dates of trial:** 13 JAN 2011 – 18 FEB 2011 | **Date of revision :** Not applicable |



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|---|---|
| **Title of trial:** | Relative bioavailability of BI 10773 given alone and together with verapamil - an open-label, randomised, crossover trial in healthy subjects |
| **Principal Investigator:** | [redacted] |
| **Trial site:** | Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine/Human Pharmacology Centre, Biberach, Germany |
| **Publication (reference):** | Data of this trial have not been published. |
| **Clinical phase:** | I |
| **Objectives:** | The objective of this trial was to study the relative bioavailability of a single dose of BI 10773 when given alone compared with the administration together with a single dose of the model P-gp inhibitor verapamil. |
| **Methodology:** | This was a randomised, open-label, crossover trial in healthy male and female subjects with 2 treatments (A and B) and 2 treatment sequences (A_B and B_A) in a single centre. Each subject received a single dose of BI 10773 in treatment A and a single dose each of BI 10773 and verapamil in treatment B. The 2 treatments were separated by a washout period of at least 7 days. |
| **No. of subjects:** | |
| **planned:** | entered: 16 male and female subjects (at least 6 of each gender) |
| **actual:** | treated: 16 subjects (8 male and 8 female subjects)<br><br>Treatment sequence A_B:<br>treated, and analysed for primary endpoint: 8 (7 male and 1 female subjects)<br>Treatment sequence B_A:<br>treated, and analysed for primary endpoint: 8 (1 male and 7 female subjects) |
| **Diagnosis and main criteria for inclusion:** | Healthy male and female volunteers in the age range of 18 to 50 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m$^2$were included. |

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|---|---|
| **Test product 1:** | BI 10773 film-coated tablet |
| **dose:** | 25 mg single dose |
| **mode of admin.:** | Oral administration with 240 mL water |
| **batch no.:** | 909473A |
| **Test product 2:** | Verapamil film-coated tablet (immediate release) |
| **dose:** | 120 mg single dose |
| **mode of admin.:** | Oral administration with 240 mL water |
| **batch no.:** | AS1341 |
| **Duration of treatment:** | Treatment A: 25 mg BI 10773 was given as a single dose.<br>Treatment B: 25 mg BI 10773 was given as a single dose 1 h after administration of a single dose of 120 mg verapamil.<br>The 2 treatments were separated by a washout period of at least 7 days. |
| **Criteria for evaluation:** | |
| **Clinical pharmacology:** | Relative bioavailability of BI 10773 was determined on the basis of the primary endpoints $AUC_{0-\infty}$ and $C_{max}$ of BI 10773.<br>The following pharmacokinetic parameters of BI 10773 served as secondary endpoints: $AUC_{0-tz}$, $t_{max}$, $\lambda_z$, $t_{1/2}$, $MRT_{po}$, CL/F, $V_z$/F.<br>In addition, verapamil plasma concentrations were determined predose and at the 1 h, 25 h, 49 h, and 73 h time points after verapamil administration. |
| **Safety:** | Safety and tolerability were determined based on monitoring of adverse events, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram, clinical laboratory assessment (haematology, coagulation, clinical chemistry, and urinalysis), physical examination, and assessment of global tolerability. |

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**Statistical methods:**

Point estimators (geometric means) of the median intrasubject ratios of $AUC_{0-\infty}$, $AUC_{0-tz}$, and $C_{max}$ of BI 10773 and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. The effect 'subjects within sequences' was considered as random, whereas the other effect were considered as fixed.

Descriptive statistics for pharmacokinetic and safety parameters were calculated.

**SUMMARY – CONCLUSIONS:**

**Clinical pharmacology results:**

All 16 entered subjects completed the trial according to the clinical trial protocol. The trial population consisted of healthy white male and female subjects. The mean age was 34.3 years, ranging from 20 to 50 years, and the mean BMI was 23.9 $kg/m^2$, ranging from 21.4 to 28.4 $kg/m^2$.

Following administration of a single oral dose of BI 10773 in combination with a single dose of verapamil or alone, plasma concentrations of BI 10773 reached peak concentrations rapidly (1.84 h and 1.59 h after drug administration, respectively) and then declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. BI 10773 exposure was similar with and without verapamil co-administration ($AUC_{0-\infty}$: 5500 nmol·h/L for combined treatment compared with 5330 nmol·h/L for BI 10773 alone; $C_{max}$: 752 nmol/L compared with 818 nmol/L). The terminal elimination half-life, oral clearance, and volume of distribution of BI 10773 were also similar when BI 10773 was given alone or in combination with verapamil ($t_{½}$: 13.6 h for combined treatment compared with 12.5·h for BI 10773 alone; CL/F: 178 ml/min compared with 184 ml/min; $V_z$/F: 204 L compared with 196 L).

Relative bioavailability of BI 10773 when given together with verapamil (test treatment) compared with BI 10773 given alone (reference treatment) was determined on the basis of the primary endpoints $AUC_{0-\infty}$ and $C_{max}$ of BI 10773. For both parameters, the gMean ratios of the test to reference treatment and the corresponding 90% CIs were within the standard bioequivalence boundaries of 80% to 125%. The gMean ratio (90% CI) was 102.95% (98.87 to 107.20%) for $AUC_{0-\infty}$ and 92.39% (85.38 to 99.97%) for $C_{max}$. Therefore, verapamil co-administration had no relevant effect on the pharmacokinetics of BI 10773. Intraindividual variability was low for both $AUC_{0-\infty}$ and $C_{max}$.

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**Safety results:**

Each of the 16 treated subjects received 2 single doses of 25 mg BI 10773 (50 mg in total) and 1 single dose of 120 mg of verapamil during the course of the trial as planned.

The number of subjects who reported at least 1 adverse event was 8 (50.0%) during treatment with BI 10773 alone (treatment A) and 9 (56.3 %) during the combined treatment with BI 10773 and verapamil (treatment B). During treatment with BI 10773 alone (treatment A), the most frequently reported adverse events at the system organ class level were nervous system disorders, experienced by 3 subjects (18.8%), and musculoskeletal and connective tissue disorders, experienced by 2 subjects (12.5%). During the combined treatment with BI 10773 and verapamil (treatment B), the most frequently reported adverse events at the system organ class level were nervous system disorders (4 subjects, 25.0%), followed by gastrointestinal disorders (3 subjects, 18.8%) and infections and infestations (2 subjects, 12.5%). The most frequently reported adverse event by preferred term in both treatment A and treatment B was headache with 3 subjects (18.8%) and 4 subjects (25.0%), respectively. No clustering of any specific adverse event in either treatment was apparent.

All adverse events reported during the treatment periods were of mild or moderate intensity. The investigator assessed 3 adverse events (dizziness, constipation, and nausea) reported by 2 subjects as related to the trial medication; all of them occurred during the combined treatment (treatment B). No serious adverse events and no adverse events leading to trial discontinuation were reported.

In this trial, there were no clinically relevant findings with respect to the clinical laboratory evaluation, vital signs, and ECG recordings. The investigator rated the overall tolerability during treatment with BI 10773 alone (treatment A) as 'good' for all 16 subjects. During the combined treatment (treatment B), the overall tolerability was rated as ' good' for 14 subjects, as 'satisfactory' for 1 subject, and as 'not satisfactory' for 1 subject.

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**Conclusions:**

Co-administration of the model P-gp inhibitor had no relevant effect on either the $AUC_{0-\infty}$ or $C_{max}$ of BI 10773, as determined by the standard bioequivalence boundaries: The gMean ratios and the corresponding 90% CIs for both $AUC_{0-\infty}$ and $C_{max}$ of BI 10773 were within 80 to 125%. These results demonstrate that there is no relevant effect of P-gp inhibition on the pharmacokinetics of BI 10773. Therefore, no dosage adjustment of BI 10773 is required when prescribed concomitantly with a P-gp inhibitor in clinical practice.

Furthermore, administration of a single dose of BI 10773 alone or in combination with a single dose of verapamil was generally well tolerated by the healthy male and female subjects in this trial.

## Trial Synopsis - Appendix

The results table on the following page supplements the trial results presented in the Trial Synopsis. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

| **Results for** | **presented in** |
|---|---|
| Pharmacokinetic parameters of BI 10773 in plasma after<br>1 tablet BI 10773 (25 mg) alone or<br>1 tablet BI 10773 + 1 tablet verapamil (120 mg) | Table 15.6.3: 1 |

Table 15.6.3: 1 Comparison of pharmacokinetic parameters of BI 10773 in plasma after single oral administration of 25 mg BI 10773 tablet alone or in combination with 120 mg verapamil tablet with descriptive statistics

| | 25 mg BI 10773 tablet | | | | 25 mg BI 10773 tablet + 120 mg verapamil tablet | | | |
|---|---|---|---|---|---|---|---|---|
| | N | gMean | gCV [%] | Mean | CV [%] | N | gMean | gCV [%] | Mean | CV [%] |
| $AUC_{0-\infty}$ [nmol*h/L] | 16 | 5190 | 25.0 | 5330 | 22.7 | 16 | 5340 | 25.5 | 5500 | 25.4 |
| $AUC_{0-tz}$ [nmol*h/L] | 16 | 5140 | 25.0 | 5280 | 22.6 | 16 | 5280 | 25.7 | 5440 | 25.4 |
| $C_{max}$ [nmol/L] | 16 | 785 | 31.5 | 818 | 27.7 | 16 | 725 | 29.1 | 752 | 27.2 |
| $t_{max}$ [h] | 16 | 1.50 | 37.0 | 1.59 | 34.8 | 16 | 1.64 | 55.0 | 1.84 | 45.6 |
| $\lambda_z$ [1/h] | 16 | 0.0573 | 29.2 | 0.0596 | 29.9 | 16 | 0.0531 | 30.2 | 0.0554 | 31.7 |
| $t_{½}$ [h] | 16 | 12.1 | 29.2 | 12.5 | 27.9 | 16 | 13.1 | 30.2 | 13.6 | 28.1 |
| $MRT_{po}$ [h] | 16 | 9.47 | 12.0 | 9.54 | 11.9 | 16 | 9.95 | 13.8 | 10.0 | 14.0 |
| CL/F [mL/min] | 16 | 178 | 25.0 | 184 | 26.8 | 16 | 173 | 25.5 | 178 | 24.8 |
| $V_z$/F [L] | 16 | 186 | 31.8 | 196 | 35.6 | 16 | 195 | 28.8 | 204 | 32.5 |

Verapamil was administered 1 h before BI 10773 administration

Source data: Section 15.6, Table 2.1: 1, 2.1: 2 pk\pksum.sas 20MAY2011