Clinical Study Synopsis for Public Disclosure

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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.

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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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-006087-11	
Name of active ingredient: BI 10773		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 JUL 2010	**Trial No. / U No.:** 1245.17 / U10-2151-02	**Dates of trial:** 08 JUN 2009 – 25 JUL 2009	**Date of revision:** 03 NOV 2011

Title of trial:	Relative bioavailability of both BI 10773 50 mg and pioglitazone 45 mg after co-administration compared to BI 10773 and pioglitazone alone in healthy male volunteers (an open-label, randomised, crossover, clinical phase I study)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objective:	The objective was to investigate whether there is a drug-drug interaction between BI 10773 and pioglitazone when co-administered as multiple oral doses. Therefore, the relative bioavailabilities of BI 10773 and pioglitazone were determined when both drugs were given in combination compared with BI 10773 and pioglitazone given alone.
Methodology:	The study was conducted according to an open-label, randomised, multiple-dose, crossover design with 3 treatments (A, B, C) and 2 treatment sequences (AB_C or C_AB). A wash-out period of at least 7 days preceded treatment C in AB_C or treatment A in C_AB.
No. of subjects:	
planned:	entered: 20
actual:	entered: 20 for each treatment Treatment A: BI 10773 50 mg once daily treated: 19 analysed (for primary endpoints): 18 Treatment B: BI 10773 50 mg once daily plus pioglitazone 45 mg once daily treated: 18 analysed (for primary endpoints): 17 Treatment C: pioglitazone 45 mg once daily treated: 20 analysed (for primary endpoints): 20
Diagnosis and main criteria for inclusion:	Healthy male subjects at the age of 18 to 50 years with a body mass index (BMI) of 18.5 to 29.9 kg/m² were included in the study.

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Test product:	BI 10773 tablets	
dose:	50 mg once daily (given as two 25 mg tablets)	
mode of admin.:	Oral	
batch no.:	B073000869	
Reference therapy:	Pioglitazone tablets (Actos®)	
dose:	45 mg once daily	
mode of admin.:	Oral	
batch no.:	3250055B (Takeda Pharma GmbH)	
Duration of treatments:	BI 10773 alone was administered for 5 days (treatment A), immediately followed by co-administration of BI 10773 and pioglitazone for 7 days (treatment B). In treatment C, pioglitazone alone was administered for 7 days. Treatments AB and C were separated by a wash-out period of at least 7 days in each treatment sequence (AB_C and C_AB).	
Criteria for evaluation:		
Clinical pharmacology:	Primary endpoints:	Pharmacokinetics: $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and pioglitazone
	Secondary endpoints:	Pharmacokinetics: $C_{24,N}$, $\lambda_{z,ss}$, $t_{½,ss}$, $t_{max,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$ of BI 10773 and pioglitazone $AUC_{\tau,ss}$, $C_{max,ss,}$ $C_{24,N}$, $\lambda_{z,ss}$, $t_{½,ss}$, $t_{max,ss}$, and $MRT_{po,ss}$ of pioglitazone metabolites (M-III and M-IV) $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, $CL_{R,ss}$ of BI 10773 Pharmacodynamics: $UGE_{0\text{-}24}$

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Safety: The safety evaluation was based on physical examinations, monitoring of vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECG), clinical laboratory tests (haematology, clinical chemistry, and urinalysis), analysis of adverse events (AEs), and assessment of tolerability by the investigator.

Statistical methods: Point estimators (geometric means [gMean]) of the median intra-subject ratios of $AUC_{\tau,ss}$ and $C_{max,ss}$ and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used for the comparison of pioglitazone (treatments B and C) was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. The model used for the comparison of treatments A and B was an ANOVA model on the logarithmic scale, with terms for 'subject' and 'treatment'. CIs were based on the residual error from ANOVA. The attainment of steady-state was investigated for BI 10773 and pioglitazone within all treatments. For $AUC_{t,ss}$, $C_{max,ss}$ and all other parameters, descriptive statistics were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results: Seventeen out of 20 randomised subjects completed study medication according to the Clinical Trial Protocol (CTP). Three subjects discontinued from the study prematurely and 1 subject discontinued after completing all study medication.

For BI 10773, there were no major differences in mean steady-state $AUC_{\tau,ss}$ and $C_{max,ss}$ when BI 10773 was administered with and without pioglitazone ($AUC_{\tau,ss}$ 8980 nmol·h/L vs. 8990 nmol·h/L, $C_{max,ss}$ 1280 nmol/L vs. 1370 nmol/L). Mean $t_{max,ss}$ of BI 10773 was approximately 2 h for either treatment.
Mean $AUC_{\tau,ss}$ and $C_{max,ss}$ of pioglitazone were higher following co-administration with BI 10773 compared to pioglitazone alone ($AUC_{\tau,ss}$ 14 000 ng·h/mL vs. 8790 ng·h/mL; $C_{max,ss}$ 1960 ng/mL vs. 1040 ng/mL). Mean $t_{max,ss}$ of pioglitazone was similar with and without co-administration.

The following table summarises the adjusted intra-individual gMean Test/Reference ratios and 90% CIs for $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and pioglitazone.

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Parameter	Test	Reference	Adjusted gMean ratio Test/Reference [%]	2-sided 90% confidence interval Lower limit [%]	Upper limit [%]
BI 10773					
$AUC_{\tau,ss}$	BI 10773+pioglitazone	BI 10773	100.32	96.08	104.75
$C_{max,ss}$	BI 10773+pioglitazone	BI 10773	93.44	85.08	102.62
Pioglitazone					
$AUC_{\tau,ss}$	BI 10773+pioglitazone	pioglitazone	157.97	148.02	168.58
$C_{max,ss}$	BI 10773+pioglitazone	pioglitazone	187.89	166.35	212.23

The results of the bioavailability analysis show that co-administration of BI 10773 with pioglitazone did not affect the extent and rate of absorption of BI 10773. Intra-individual variability between the treatments was low for $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 (geometric coefficients of variation [gCV] 7.3% and 15.9%).
Co-administration of pioglitazone with BI 10773 resulted in higher exposure of pioglitazone compared to pioglitazone alone. $AUC_{\tau,ss}$ and $C_{max,ss}$ of pioglitazone increased by approximately 58% and 88% with co-administration . For $AUC_{\tau,ss}$ of pioglitazone, the intra-individual gCV was 10.8% and for $C_{max,ss}$ of pioglitazone the intra-individual gCV was 20.7%.

Plasma levels of 2 active metabolites of pioglitazone, M-III (keto derivative of pioglitazone) and M-IV (hydroxy derivative of pioglitazone), were also higher following administration of pioglitazone with BI 10773 compared to pioglitazone alone. Descriptive statistics estimated using 17 subjects who completed both treatments show that mean $AUC_{\tau,ss}$ and $C_{max,ss}$ were approximately 28% and 26% higher in case of M-III and 27% and 33% higher in case of M-IV. The terminal elimination half-lives of both metabolites were similar with and without co-administration. The overall exposure (AUC) to pharmacologically active moieties (estimated by pooling $AUC_{\tau,ss}$ values of pioglitazone and its 2 active metabolites) increased by approximately 36% following co-administration with BI 10773.

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The cumulative amounts of BI 10773 excreted in urine were not affected by co-administration. In addition, the increased urinary glucose excretion observed with BI 10773 administration was not affected by pioglitazone co-administration. The total amounts of glucose excreted in urine were similar when BI 10773 was administered with and without pioglitazone (77.5 g and 74.9 g).

Safety results:

Three out of 20 subjects (each treatment sequence C_AB) discontinued from the study:
Subject [redacted] was withdrawn by the investigator due to a general lack of compliance. Subject [redacted] terminated the trial at his own wish due to an adverse event (gastroenteritis). Subject [redacted] was withdrawn from the trial due to an adverse event (blood creatine phosphokinase increase due to excessive sports).

17/20 subjects received a total dose of 600 mg of BI 10773 and a total dose of 630 mg of pioglitazone during the trial as planned. 3/20 subjects of treatment sequence C_AB received the following doses of study medication: 315 mg pioglitazone (Subject [redacted]), 495 mg pioglitazone + 450 mg BI 10773 (Subject [redacted]) , 315 mg pioglitazone + 50 mg BI 10773 (Subject [redacted]).

9/20 subjects (45.0%) reported at least 1 AE during the trial: 1/19 subjects (5.3%) during treatment with BI 10773 alone, 5/18 subjects (27.8%) during the combined treatment, and 4/20 subjects (20.0%) during treatment with pioglitazone alone.

Drug-related AEs were reported by 20.0% of subjects (4/20 subjects): 1/19 subjects (5.3%) under BI 10773 alone (anorexia) and 3/20 subjects (15.0%) under pioglitazone alone (2 cases of headache, 1 case of increased appetite). No drug-related AEs were reported under combination treatment with BI 10773+pioglitazone.

Headache was the most frequently reported AE overall during the treatment phase, experienced by 2/20 subjects (10.0%). Headache was reported only during pioglitazone treatment alone and was assessed as drug-related in both cases. Other AEs occurring during the trial were reported by only 1 subject each (5.0%).

All reported AEs were of mild or moderate intensity. No serious AEs occurred in this trial. One subject needed specific treatment because of an AE (conjunctivitis) and all subjects recovered fully.

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Other significant AEs that led to discontinuation were reported by 2/20 subjects (10.0%): gastroenteritis (BI 10773 + pioglitazone) and increased blood creatine phosphokinase (after pioglitazone alone). Both events were regarded as unrelated to study medication.

Overall tolerability was assessed as 'good' for all subjects experiencing the treatment periods: 20 subjects completing pioglitazone alone, 18 subjects receiving BI 10773 alone, and 18 subjects receiving combined BI 10773 and pioglitazone.
There were no clinically relevant findings with respect to the evaluation of laboratory parameters, vital signs, and ECG recordings.

Conclusions:

Pioglitazone co-administration had no clinically relevant effect with respect to the standard bioequivalence boundaries on either the extent or rate of absorption of BI 10773. BI 10773 co-administration resulted in higher pioglitazone exposure. $AUC_{\tau,ss}$ and $C_{max,ss}$ of pioglitazone increased by approximately 58% and 88% following co-administration with BI 10773 compared to pioglitazone alone. The overall exposure to pharmacologically active moieties (pioglitazone plus 2 active metabolites) increased by approximately 36% following co-administration of pioglitazone with BI 10773 compared to pioglitazone alone. At this point, there is no clear mechanistic explanation for the observed interaction between BI 10773 and pioglitazone.

Overall, relative bioavailability of BI 10773 was similar following co-administration compared to BI 10773 alone at steady-state. The clinical relevance of the interaction observed in terms of increased pioglitazone exposure following co-administration with BI 10773 is unknown.

Furthermore, multiple daily doses of 50 mg BI 10773 and 45 mg pioglitazone were well tolerated when given either alone or in combination to healthy male subjects.