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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-018089-36	
Name of active ingredients: BI 10773 + Pioglitazone		**Page:** 1 of 6	**Synopsis No.:**
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Report date: 22 FEB 2011	**Trial No. / U No.:** 1245.50 / U11-1194-01	**Dates of trial:** 09 APR 2010 – 16 JUL 2010	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of pioglitazone after co-administration with different doses of BI 10773 in healthy volunteers (an open-label, randomised, crossover, clinical phase I study)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG Biberach an der Riss, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objective:	The objective was to investigate the effect of different doses of BI 10773 on the bioavailability of pioglitazone after multiple oral doses of both drugs.
Methodology:	This was an open-label, randomised, multiple-dose, cross-over study with 4 treatments (A, B, C, and D) in 4 sequences (ADBC, BACD, CBDA, and DCAB).
No. of subjects:	
planned:	entered: 20

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actual:	entered: 20 Treatment A: Pioglitazone 45 mg q.d. on Days 1 to 7, entered: 20 treated: 20 analysed (for primary endpoint): 19 Treatment B: Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 10 mg q.d. on Days 1 to 9, entered: 20 treated: 18 analysed (for primary endpoint): 18 Treatment C: Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 25 mg q.d. on Days 1 to 9, entered: 20 treated: 17 analysed (for primary endpoint): 17 Treatment D: Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 50 mg q.d. on Days 1 to 9, entered: 20 treated: 16 analysed (for primary endpoint): 16 Treatment E: Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 25 mg q.d. given 1 h after pioglitazone on Days 1 to 9 entered: 20 treated: 0 analysed (for primary endpoint): 0* Treatment F: Pioglitazone 30 mg q.d. on Days 1 to 7 + BI 10773 50 mg q.d. on Days 1 to 9 entered: 20 treated: 0 analysed (for primary endpoint): 0* *Treatments E and F were optional and were not performed based on an interim analysis of the results of Treatments A, B, C, and D.
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 55 years, body mass index 18.5 to 29.9 kg/m^2
Trial product 1:	BI 10773 tablet
dose:	10 mg, 25 mg, 50 mg
mode of admin.:	Oral
batch no.:	10 mg: 909475A 25 mg: 909473A

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Trial product 2:	Pioglitazone tablet (Actos®)
dose:	45 mg once daily
mode of admin.:	Oral
batch no.:	4250009D
Duration of treatment:	Pioglitazone was administered for 7 days each in Treatments A, B, C, and D for a total of 28 days. Each treatment was followed by a wash-out period of at least 8 days. BI 10773 was administered for 9 days each in Treatments B, C, and D for a total of 27 days. Each treatment was followed by a wash-out period of at least 6 days.
Criteria for evaluation:	
Pharmacokinetics:	*Primary endpoints* Pioglitazone at steady state: $AUC_{\tau,ss}$ and $C_{max,ss}$ *Secondary pharmacokinetic (PK) endpoints* Pioglitazone at steady state: $C_{24,N}$, $\lambda_{z,ss}$, $t_{½,ss}$, $t_{max,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$, $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, and $CLR_{,ss}$ Pioglitazone after a single dose: $AUC_{0\text{-}tz}$, $AUC_{\tau,1}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{½}$, λ_z, CL/F, V_z/F, MRT_{po}, $Ae_{t1\text{-}t2}$, $fe_{t1\text{-}t2}$, and CL_R Pioglitazone metabolites M-III and M-IV at steady state: $AUC_{\tau,ss}$, $C_{max,ss}$, $C_{24,N}$, $\lambda_{z,ss}$, $t_{½,ss}$, $t_{max,ss}$, $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, $CLR_{,ss}$, and metabolite-to-parent ratio (AUC and C_{max}) Pioglitazone metabolites M-III and M-IV after a single dose: $AUC_{0\text{-}tz}$, $AUC_{\tau,1}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{½}$, λ_z, $Ae_{t1\text{-}t2}$, $fe_{t1\text{-}t2}$, CL_R, and metabolite-to-parent ratio (AUC and C_{max}) BI 10773: $C_{24,N}$

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Safety:	*Secondary safety endpoints* • Physical examination • Vital signs (blood pressure and pulse rate) • 12-lead electrocardiogram (ECG) • Clinical laboratory tests (haematology, clinical chemistry, and urinalysis) • Adverse events • Assessment of tolerability by investigator
Statistical methods:	For the comparison of Treatments B, C, and D with Treatment A, relative bioavailability was evaluated by calculating the point estimators (geometric means) of the median intra-subject ratios of $AUC_{\tau,ss}$ and $C_{max,ss}$ for pioglitazone and its metabolites and their 2-sided 90% confidence intervals. The statistical model was analysis of variance (ANOVA) on log-transformed parameters. The model included effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Descriptive statistics were calculated for all parameters.
SUMMARY – CONCLUSIONS:	
Pharmacokinetics results:	*Subject disposition, analysis sets, and baseline characteristics* Fifteen of the 20 randomised subjects completed the trial as planned. Reasons for not completing the trial were adverse events in 2 subjects, non-compliance with the protocol in 2 subjects, and withdrawal of consent in 1 subject. No important protocol violations were reported. All 20 subjects were included in both the treated set and the PK analysis set. Demographic data of the subjects in the 4 sequences were balanced. The overall mean age, height, weight, and body mass index were 33.9 years, 178.0 cm, 77.7 kg, and 24.49 kg/m^2. No relevant medical history or concomitant diagnoses were reported. Concomitant therapies were reported in 7 subjects (35.0%).

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Pharmacokinetics results (continued):

Primary endpoints

After multiple oral administration of 45 mg pioglitazone q.d., the mean $AUC_{\tau,ss}$ of pioglitazone was 10500 ng·h/mL (coefficient of variation [CV] 38.2%) and the mean $C_{max,ss}$ 1260 ng/mL (CV 60.9%). When pioglitazone was co-administered with 10 mg, 25 mg, or 50 mg BI 10773, steady state exposure to pioglitazone was slightly lower – the mean $AUC_{\tau,ss}$ ranged from 8820 to 9200 ng·h/mL (CV 22.0 to 39.7%). and the mean $C_{max,ss}$ ranged from 988 to 1110 ng/mL (CV 29.3 to 60.1%).

Geometric mean ratios for pioglitazone $AUC_{\tau,ss}$ and $C_{max,ss}$ ranged from 88% to 91%. The lower limits of the 90% confidence intervals ranged from 67% to 78%, below the standard bioequivalence boundaries of 80% to 125%. The upper limits, ranging from 104% to 122%, were within the standard bioequivalence boundaries.

Secondary PK endpoints

After a single dose of 45 mg pioglitazone, rate and extent of pioglitazone exposure were similar when pioglitazone was given with 10, 25, or 50 mg BI 10773 (AUC_{0-24} 8410 to 8960 ng•h/mL, CV 33.1%; C_{max} 924 to 1020 ng/mL, CV 37.3 to 38.0%) and when pioglitazone was given alone (AUC_{0-24} 8670 ng•h/mL, CV 28.2%; C_{max} 908 ng/mL, CV 35.5%). The time to reach peak plasma concentrations (t_{max}) of pioglitazone remained approximately 2 h and other PK parameters were also similar with and without BI 10773. Variability was moderate.

At steady state, the apparent clearance ($CL/F_{,ss}$) of pioglitazone was slightly higher when 45 mg pioglitazone q.d. was co-administered with BI 10773 (90.1 to 95.4 mL/min, CV 27.7 to 43.0%) than when pioglitazone was given alone (82.3 mL/min, CV 39.8%). The apparent volume of distribution ($V_z/F_{,ss}$) of pioglitazone was also higher with BI 10773 (95.6 to 110 L) than without (85.4 L) but variability was high (CV 61.8 to 85.4%).

Exposure to the pioglitazone metabolites M-III and M-IV and the elimination of both metabolites were similar when pioglitazone was given with and without BI 10773, both after a single dose and at steady state. Urine concentrations of pioglitazone and M-III were generally below the limit of quantitation. Very low levels of M-IV were detected in urine.

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Safety results:

Seventeen of the 20 subjects reported at least one adverse event. The frequency of subjects with adverse events was similar when 45 mg pioglitazone q.d. was administered alone (40.0%) and with 10 mg (55.6%), 25 mg (29.4%), and 50 mg BI 10773 q.d. (37.5%). The most frequently reported adverse event overall was headache, reported in 9 subjects (45.0%).

No serious adverse events were reported.

One subject discontinued treatment with the study medications (pioglitazone alone) due to adverse events (nausea and vomiting). In addition, one subject was not treated with pioglitazone + BI 10773 50 mg (the third of his 4 treatments) due to arthralgia that occurred during washout of the previous treatment.

The investigator considered adverse events in 13 subjects (65.0%) possibly related to the study medication. The most frequently reported drug-related adverse event was headache, reported in 7 subjects during the trial.

All adverse events were of mild or moderate intensity.

There were no clinically signficant changes in clinical laboratory parameters or vital signs. No ECG findings were reported as adverse events.

Global tolerability was assessed as ‘satisfactory’ in 2 subjects (11.8%) after treatment with pioglitazone and 25 mg BI 10773 and ‘good’ in all other subjects after all other treatment periods.

Conclusions:

Co-administration of BI 10773 with pioglitazone resulted in a slight reduction in the both the rate and extent of absorption of pioglitazone at steady state. The extent of exposure of 2 pharmacologically active metabolites of pioglitazone, M-III and M-IV, was similar when pioglitazone was given with and without BI 10773. With regard to safety, BI 10773 had no effect on the frequency or intensity of adverse events in subjects treated with pioglitazone. Therefore, no dose of BI 10773 tested in this trial was found to have a clinically relevant effect on pioglitazone plasma levels and no dosage adjustment of pioglitazone is required when this drug is concomitantly prescribed with BI 10773.