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.

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.:** 2008-006059-38	
Name of active ingredient: BI 10773		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 07 SEP 2009	**Trial No. / U No.:** 1245.6 / U09-1852-01	**Dates of trial:** 15 JAN 2009 – 03 MAR 2009	**Date of revision** (if applicable)**:**

Title of trial:	Relative bioavailability of both BI 10773 and metformin after co-administration compared to multiple oral doses of BI 10773 (50 mg q.d.) alone and metformin (1000 mg b.i.d.) alone to 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 a possible drug-drug interaction between BI 10773 and metformin when co-administered as multiple oral doses. Therefore, the relative bioavailabilities of BI 10773 and metformin were determined when both drugs were given in combination compared with BI 10773 or metformin 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: 16
actual:	entered: 16
	Treatment A: BI 10773 50 mg once daily treated: 16 analysed (for primary endpoints): 16
	Treatment B: BI 10773 50 mg once daily plus metformin 1000 mg twice daily treated: 16 analysed (for primary endpoints): 16
	Treatment C: metformin 1000 mg twice daily treated: 16 analysed (for primary endpoints): 15
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:	Metformin tablets
dose:	1000 mg twice daily
mode of admin.:	Oral
batch no.:	200847 / 201180 (Merck Pharma GmbH)
Duration of treatments:	BI 10773 was administered for 5 days (treatment A), immediately followed by co-administration of BI 10773 and metformin over 4 days (treatment B). In treatment C, metformin was administered for 4 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: $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and metformin Secondary endpoints: $C_{24,N}$ of BI 10773, $C_{12,N}$ of metformin, $\lambda_{z,ss}$, $t_{½,ss}$, $t_{max,ss}$, $MRT_{po,ss}$, CL/F_{ss}, V_z/F_{ss}, $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, $CL_{R,ss}$ of BI 10773 and metformin, urinary glucose excretion
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 an 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 for the investigation of 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'. CIs were based on the residual error from the ANOVA. The statistical model used for the investigation of treatments A and B was an ANOVA model on the logarithmic scale including effects for 'subject' and

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'treatment'. The effect 'subject' was considered as random, whereas the effect 'treatment' was considered as fixed. The attainment of steady-state was investigated for both BI 10773 and metformin. For all other parameters, descriptive statistics were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

All 16 randomised subjects completed the trial according to the Clinical Trial Protocol. Since 1 subject experienced vomiting during treatment with metformin alone (at about 1.5 h post-dose on Day 4), the subject's data for this period were excluded from the analyses.

For BI 10773, mean steady-state $AUC_{\tau,ss}$ and $C_{max,ss}$ were comparable when BI 10773 was administered with and without metformin ($AUC_{\tau,ss}$ 9540 nmol·h/L vs. 9810 nmol·h/L; $C_{max,ss}$ 1400 nmol/L vs. 1340 nmol/L). Mean $t_{max,ss}$ of BI 10773 was approximately 1.5 h for either treatment. Mean $AUC_{\tau,ss}$ and $C_{max,ss}$ of metformin were also comparable with and without BI 10773 co-administration ($AUC_{\tau,ss}$ 8490 ng·h/mL vs. 8660 ng·h/mL; $C_{max,ss}$ 1570 ng/mL vs. 1530 ng/mL). Mean $t_{max,ss}$ of metformin was 1.8 h when co-administered with BI 10773 and 1.4 h when metformin was administered alone.

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

Parameter	Test	Reference	Adjusted gMean ratio Test/Reference [%]	2-sided 90% confidence interval Lower limit [%]	Upper limit [%]
BI 10773					
$AUC_{\tau,ss}$	BI 10773+metformin	BI 10773	96.88	92.29	101.70
$C_{max,ss}$	BI 10773+metformin	BI 10773	100.45	88.76	113.70
Metformin					
$AUC_{\tau,ss}$	BI 10773+metformin	Metformin	100.67	95.93	105.64
$C_{max,ss}$	BI 10773+metformin	Metformin	103.59	96.52	111.18

The results of the bioavailability analysis show that co-administration of BI 10773 with metformin did not affect the extent and rate of absorption of

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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] 7.8% and 20.2%, respectively). Co-administration of both drugs did not affect the extent and rate of absorption of metformin either. For $AUC_{\tau,ss}$ of metformin, the intra-individual gCV was 7.5%, for $C_{max,ss}$ of metformin, the intra-individual gCV was 11.0%. The extent and rate of absorption met the bioequivalence criteria of 80 to 125% for both BI 10773 and metformin.

The cumulative amounts of BI 10773 and metformin excreted in urine were not affected by co-administration. In addition, there were no relevant differences in the mean cumulative amounts of glucose excreted in urine when BI 10773 was administered with and without metformin (62.0 g and 67.8 g, respectively).

Safety results:

All 16 subjects received a total dose of 450 mg BI 10773 and a total dose of 14 000 mg metformin during the trial as planned.

Twelve subjects (75.0%) reported at least 1 AE: 5 subjects (31.3%) during treatment with BI 10773 alone, 7 subjects (43.8%) during the combined treatment, and 11 subjects (68.8%) during treatment with metformin alone.

The most frequently reported AEs overall were diarrhoea (43.8%), headache (37.5%), and nausea (25.0%). The incidence of diarrhoea was highest during treatment with metformin alone (6 subjects), followed by BI 10773 plus metformin (2 subjects), and BI 10773 alone (1 subject). Headache was experienced by 3 subjects each under BI 10773 alone and under metformin alone. Nausea was reported by 4 subjects during treatment with metformin alone and by 1 subject during the combined treatment. The majority of AEs with only few exceptions were defined as drug-related by the investigator. Diarrhoea, headache, and nausea were assessed as drug-related in all cases.

Most AEs were of mild or moderate intensity, only 1 subject experienced an AE of severe intensity: nausea under metformin treatment. This subject also experienced vomiting in the same treatment period. No serious AEs and no AEs leading to discontinuation occurred in this trial. None of the AEs required therapy.

Overall tolerability was assessed as 'good' for all subjects in each treatment period. There were no clinically relevant findings with respect to the evaluation of laboratory parameters, vital signs, and ECG recordings.

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Conclusions:

Metformin co-administration had no clinically relevant effect with respect to the standard bioequivalence boundaries on both extent and rate of absorption of BI 10773. Similarly, BI 10773 co-administration had no clinically relevant effect on both extent and rate of absorption of metformin. At steady-state, relative bioavailabilities of BI 10773 and metformin were similar following co-administration compared to BI 10773 alone and metformin alone. The results demonstrate that there is no drug-drug interaction between BI 10773 and metformin.

Furthermore, multiple daily doses of 50 mg BI 10773 and 2000 mg metformin were well tolerated when either given alone or in combination to healthy subjects.