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.:** 2008-006060-11	
Name of active ingredient: BI 10773		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 FEB 2010	**Trial No. / U No.:** 1245.7 / U10-1197-02	**Dates of trial:** 22 APR 2009 – 12 JUN 2009	**Date of revision:** 21 DEC 2011

Title of trial:	Relative bioavailability of both BI 10773 and glimepiride after co-administration compared to multiple oral doses of BI 10773 (50 mg q.d.) alone and a single dose of glimepiride (1 mg) 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 was a drug-drug interaction between BI 10773 and glimepiride when co-administered. Therefore, the relative bioavailabilities of BI 10773 and glimepiride were determined when both drugs were given in combination compared to multiple oral doses of BI 10773 once daily alone and a single oral dose of glimepiride 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 plus glimepiride 1 mg as single dose treated: 16 analysed (for primary endpoints): 16 Treatment C: glimepiride 1 mg as single dose treated: 16 analysed (for primary endpoints): 16
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:	Glimepiride tablets (Amaryl®)
dose:	1 mg as single dose at two occasions
mode of admin.:	Oral
batch no.:	B081004979 (Sanofi-Aventis Deutschland GmbH)
Duration of treatments:	BI 10773 was administered for 5 days (treatment A), immediately followed by co-administration of BI 10773 and glimepiride for 1 day (treatment B). In treatment C, glimepiride was administered for 1 day. 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 pharmacokinetic endpoints: $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and $AUC_{0-\infty}$ and C_{max} of glimepiride Secondary pharmacokinetic endpoints: AUC_{0-tz}, t_{max}, λ_z, $t_{½}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, CL_R of glimepiride $t_{max,ss}$, $\lambda_{z,ss}$, $t_{½,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$, $Ae_{t1-t2,ss}$, $fe_{t1-t2,ss}$, $CL_{R,ss}$ of BI 10773
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, urinalysis), blood glucose bedside tests, and the analysis of adverse events (AEs).
Statistical methods:	Point estimators (geometric means [gMean]) of the median intra-subject ratios of $AUC_{\tau,ss}$ or $AUC_{0-\infty}$ and $C_{max,ss}$ or C_{max} and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used for the comparison of glimepiride (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'.

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The model used for the comparison of BI 10773 (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. 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.

For BI 10773, mean steady-state $AUC_{\tau,ss}$ and $C_{max,ss}$ were comparable when BI 10773 was administered without and with glimepiride ($AUC_{\tau,ss}$ 9370 nmol·h/L vs. 8910 nmol·h/L; $C_{max,ss}$ 1350 nmol/L vs. 1280 nmol/L). Mean $t_{max,ss}$ of BI 10773 was 1.75 h and 1.66 h when BI 10773 was administered without and with glimepiride . Mean $AUC_{0-\infty}$ and C_{max} of glimepiride were also comparable without and with BI 10773 co-administration ($AUC_{0-\infty}$ 233 ng·h/mL vs. 218 ng·h/mL, $C_{max,ss}$ 47.4 ng/mL vs. 47.6 ng/mL). Mean t_{max} of glimepiride was 2.50 h when administered alone and 1.69 h when co-administered with BI 10773.

The following table summarises the gMean Test/Reference ratios and 90% CIs for $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 10773 and $AUC_{0-\infty}$ and C_{max} of glimepiride.

Parameter	Test	Reference	gMean ratio	2-sided 90% confidence interval	
			Test/Reference [%]	Lower limit [%]	Upper limit [%]
BI 10773					
$AUC_{\tau,ss}$	BI 10773+glimepiride	BI 10773	95.23	92.03	98.54
$C_{max,ss}$	BI 10773+glimepiride	BI 10773	95.55	88.24	103.46
Glimepiride					
$AUC_{0-\infty}$	BI 10773+glimepiride	Glimepiride	93.26	86.08	101.04
C_{max}	BI 10773+glimepiride	Glimepiride	104.18	89.47	121.30

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The results of the bioavailability analysis show that co-administration of BI 10773 with glimepiride 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] 5.5% and 12.9%, respectively). Co-administration of both drugs did not affect the extent and rate of absorption of glimepiride either. For $AUC_{0-\infty}$ of glimepiride, the intra-individual gCV was 12.9%; for C_{max} of glimepiride, the intra-individual gCV was 24.8%. The extent and rate of absorption met the bioequivalence criteria of 80 to 125% for both BI 10773 and glimepiride.

For glimepiride, urine PK parameters were not calculated, as glimepiride urine concentrations were below the limit of quantification in all subjects except in one subject. The cumulative amounts of BI 10773 excreted in urine (UGE_{0-24}) were not affected by co-administration (20.0% of dose without vs. 20.5% of dose with 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 glimepiride (72.7 g and 68.7 g, respectively).

Safety results:

All 16 subjects received a total dose of 300 mg BI 10773 and a total dose of 2 mg glimepiride during the trial as planned.

Five subjects (31.3%) reported at least 1 AE: 3 subjects (18.8%) during treatment with BI 10773 alone, 1 subject (6.3%) during the combined treatment, and 4 subjects (25.0%) during treatment with glimepiride alone.

The incidence of drug-related AEs was equally distributed among treatment with BI 10773 and glimepiride alone, respectively: 2 subjects (12.5%) under each treatment (3 cases of headache and 1 case of fatigue). Headache was the most frequently reported AE overall (18.8% of all subjects) and was assessed as drug-related in all cases. Headache was reported by 1 subject (6.3%) under BI 10773 treatment alone and by 2 subjects (12.5%) under glimepiride treatment alone. Drug-related fatigue was reported by 1 subject (6.3%) taking BI 10773 alone. Other AEs occurring during the trial were reported by only 1 subject each (6.3%).

All reported AEs were of mild or moderate intensity. No serious AEs, no other significant AEs, and no AEs leading to discontinuation occurred in this trial. Two subjects (12.5%) needed specific treatment because of AEs (two drug-related headaches of moderate intensity). All subjects recovered fully.

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	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, glucose bedside test results, vital signs, and ECG recordings.
Conclusions:	Glimepiride co-administration had no clinically relevant effect on either the extent or rate of absorption of BI 10773, as determined by the standard bioequivalence boundaries. Similarly, BI 10773 co-administration had no clinically relevant effect on either the extent or rate of absorption of glimepiride. Relative bioavailabilities of BI 10773 and glimepiride were similar following co-administration compared to administration of BI 10773 alone and glimepiride alone. The results demonstrate that there is no drug-drug interaction between BI 10773 and glimepiride. Furthermore, multiple daily doses of 50 mg BI 10773 and a single dose of 1 mg glimepiride were well tolerated when given either alone or in combination to healthy male subjects.