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.

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Not applicable				
Name of active ingredient: BI 10773		**Page:**	**Number:**	
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Report date: 08 April 2008	**Number:** U08-1237-02	**Study period (dates):** 11 Jan 07 – 29 Mar 07		**Revision date:** 23 January 2009

Title of study:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses (0.5 mg to 800 mg) of BI 10773 as tablets administered to healthy male subjects. A randomised, placebo-controlled (within dose groups) and double-blind trial.
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 10773
Methodology:	Randomised, double-blind, placebo-controlled within dose groups, single rising dose, single centre
No. of subjects:	
planned:	entered: 72
actual:	enrolled: 72 BI 10773: entered: 54 treated: 52 analysed (for primary endpoint): 52 Placebo: entered: 18 treated: 18 analysed (for primary endpoint): 18
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 50 years, BMI 18.5 to 29.9 kg/m^2
Test product:	BI 10773 as tablets
dose:	0.5 mg, 2.5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg
mode of admin.:	Taken by mouth (p.o.) with 240 mL water, in fasted state at all doses in the single rising dose (SRD) part and under oral glucose tolerance test (OGTT) conditions at the 50 mg dose in the OGTT part

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batch no.:	0.5 mg tablet (for 0.5 mg and 2.5 mg doses): B061002447 5 mg tablet (for 10 mg dose): B061002448 25 mg tablet (for 25 mg and 50 mg doses): B061002449 100 mg tablet (for 100 mg, 200 mg, 400 mg, and 800 mg doses): B061002450
Duration of treatment:	Single dose
Reference therapy:	Matching placebo as tablets
dose:	—
mode of admin.:	Taken p.o. with 240 mL water, in the fasted state (SRD part) or under OGTT conditions (OGTT part)
batch no.:	Placebo for 0.5 mg and 5 mg tablet: B061002444 Placebo for 25 mg tablet: B061002445 Placebo for 100 mg tablet: B061002446
Criteria for evaluation:	
Efficacy:	Pharmacokinetic (PK) parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$; parameters for metabolite were to be calculated if sufficient data were available. Pharmacodynamic (PD) parameter: urinary glucose excretion (UGE) Biomarker: plasma glucose
Safety:	Tolerability, adverse events (AEs), physical examination, vital signs (blood pressure, heart rate), 12-lead electrocardiogram (ECG), and laboratory tests
Statistical methods:	Descriptive statistics for safety, PK and PD endpoints were calculated. Dose proportionality of BI 10773 was explored using a regression model. A 95% confidence interval for the slope of log- transformed parameters (AUC, C_{max}) was computed.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Not applicable.

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Pharmacokinetic results:	Single oral doses of 0.5 to 800 mg BI 10773 were rapidly absorbed, reaching peak levels in 1.5 to 2.5 h. Plasma concentration time profiles showed a biphasic decline, i.e. a rapid distribution phase and a slower elimination phase. The mean terminal elimination half-life ranged from 8.57 to 13.1 h. Increases in BI 10773 exposure (AUC and C_{max}) were approximately proportional with dose from 0.5 to 800 mg. Oral clearance was moderate (221 to 429 mL/min). Oral administration of glucose had no relevant effect on the pharmacokinetics of BI 10773. The amount of drug excreted unchanged in the urine ranged from 11.0% to 18.7% of the administered dose of BI 10773. EX 609, an active metabolite of BI 10773, was not detected in plasma after single oral doses of 0.5 to 50 mg BI 10773; only partial profiles were obtained at doses of 100 to 800 mg BI 10773. EX 609 exposure appeared to increase with BI 10773 dose; however, no consistent trends were observed to define dose proportionality. At the highest dose level, metabolite exposure (AUC and C_{max}) was approximately 0.12% of that of the parent drug. The total fraction of EX 609 in urine ranged from 0.02 to 0.05% of the administered dose of BI 10773.
Pharmacodynamic results:	Increased urinary glucose excretion compared with placebo was observed at all doses of BI 10773. The amount of glucose excreted increased sharply at lower doses and reached a plateau at higher doses. With a 5-fold increase in dose from 0.5 to 2.5 mg BI 10773, the amount of glucose excreted in urine in the first 24 h increased about 10-fold to 30600 mg, compared with 58.0 mg with placebo. After treatment with 50 to 800 mg BI 10773, the amount of glucose excreted in urine in the first 24 h ranged from 61600 to 90800 mg. The duration of effect increased with dose. At doses less than 50 mg BI 10773, the majority of glucose was excreted in the first 24 h; after treatment with 2.5 mg BI 10773, 33000 mg of glucose was recovered in urine from 0 to 72 h, compared with 191 mg after placebo. At higher doses, further increases in glucose excretion were observed up to the last urine collection interval, 48-72 h. The total amount of glucose excreted over 72 h reached a plateau of 177000 to 211000 mg glucose over the dose range of 100 to 800 mg. The increase in the amount of glucose excreted could be attributed to increases in the rate of glucose excretion following BI 10773 administration. The rate of urinary glucose excretion increased sharply with dose up to 10 mg BI 10773 and reached a plateau over the dose range 10 to 800 mg. The time to reach maximum excretion rate was about 7 h in most subjects and was similar in all dose groups. Under the controlled high fluid intake conditions of this trial, urine volumes were similar in all treatment groups. Increase in UGE had no relevant effect on plasma glucose levels.

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	In the OGTT part, glucose intake following single doses of 50 mg BI 10773 resulted in more than 200-fold increases in both amount and rate of glucose excretion compared with OGTT alone. Mean AUEC values of glucose in plasma were similar with and without administration of BI 10773 and mean peak plasma glucose levels were only slightly reduced by treatment with 50 mg BI 10773.
Safety results:	After administration of single doses of 0.5 to 800 mg BI 10773 or matching placebo to healthy male volunteers, the number of subjects who experienced AEs was similar between subjects treated with any dose of BI 10773 and with placebo (25.0% *vs* 22.2%). Under OGTT conditions, the number of subjects who experienced AEs after a single dose of 50 mg BI 10773 was not greater than with placebo. The most frequently reported AE was headache; the number of subjects with headache was similar between subjects treated with any dose of BI 10773 and with placebo (13.5% *vs* 11.1%). No trends in AEs with respect to dose were observed. Most AEs were considered mild in intensity and most subjects recovered from the AEs. No serious AEs or deaths occurred. There were no findings of clinical significance in the clinical laboratory evaluation, vital signs, 12 lead ECG, or global tolerability. The total amount of creatinine excreted in urine was similar in all dose groups, indicating that increased urinary glucose excretion did not affect renal function during the study period.
Conclusions:	BI 10773 was rapidly absorbed following oral administration and showed a biphasic decline. Increases in exposure were approximately proportional with dose from 0.5 to 800 mg BI 10773. The terminal elimination half-life ranged from 8.57 to 13.1 h. Oral clearance was moderate (221 to 429 mL/min). The amount of drug excreted unchanged in the urine ranged from 11.0% to 18.7% of the administered dose of BI 10773. The rate and amount of urinary glucose excretion increased with increasing dose of BI 10773. The increased UGE had no relevant effect on plasma glucose levels and did not affect renal function. Single oral doses of 0.5 to 800 mg BI 10773 were safe and well tolerated in healthy male volunteers. The results of this study do not indicate any safety concerns for future clinical trials of BI 10773.