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			
Name of active ingredient: BI 10773		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 2 Mar. 2009	**Trial No. / U No.:** 1245.5 / U09-3056-01	**Date of trial:** 18 JUN 2008 – 18 AUG 2008	**Date of revision** (if applicable)**:**

Title of trial:	A Phase I, randomised, double-blind, placebo-controlled (within dose groups) study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses (1 to 100 mg) of BI 10773 in healthy male volunteers
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted] [redacted] Japan
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 10773 administered to healthy Japanese male subjects with single rising oral doses (1, 5, 10, 25, and 100 mg)
Methodology:	Randomised, double-blind, placebo-controlled within dose groups, single-rising-dose, single−centre trial
No. of subjects:	
planned:	to be entered: 48 subjects
actual:	enrolled: 132 subjects, entered: 48 subjects Treatment with BI 10773 1 mg: entered, 6 subjects; treated, 6 subjects; analysed (for primary endpoint), 6 subjects Treatment with BI 10773 5 mg: entered, 6 subjects; treated, 6 subjects; analysed (for primary endpoint), 6 subjects Treatment with BI 10773 10 mg: entered, 12 subjects; treated, 12 subjects (6 with oral glucose tolerance tests [oGTT]); analysed (for primary endpoint), 12 subjects Treatment with BI 10773 25 mg: entered, 6 subjects; treated, 6 subjects; analysed (for primary endpoint), 6 subjects

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actual (continued)	Treatment with BI 10773 100 mg: entered, 6 subjects; treated, 6 subjects; analysed (for primary endpoint), 6 subjects Treatment with placebo: entered, 12 subjects; treated, 12 subjects; (2 with an oGTT) analysed (for primary endpoint), 12 subjects
Diagnosis and main criteria for inclusion:	Healthy male volunteers; age: ≥20 and ≤35 years; body mass index range: ≥18.0 and ≤25.0 kg/m^2
Test product:	BI 10773 tablets: 1 mg, 5 mg, and 25 mg
dose:	1, 5, 10, 25, and 100 mg once daily
mode of admin.:	oral, taken fasted with approximately 150 mL water
batch no.:	PR08/30036
Reference therapy:	Matching placebo as tablets
dose:	Not applicable
mode of admin.:	oral, taken fasted with approximately 150 mL water
batch no.:	PR08/30036
Duration of treatment:	Single dose
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Pharmacodynamics:	Pharmacodynamic parameter: glucose in the urine Biomarker: glucose in plasma
Safety:	Adverse events, clinical laboratory tests including renal function parameters (N-acetyl-ß-D-glucosaminidase, urinary microalbumin to creatinine ratio, and α_1-microglobulin), vital signs (blood pressure, pulse rate, and body temperature), 12-lead electrocardiography, and tolerability

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Statistical methods: Descriptive statistics were calculated for the safety, tolerability, pharmacokinetics, and pharmacodynamics. Dose proportionality of BI 10773 was explored by using a regression model. A 95% confidence interval for the slope was computed.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Pharmacokinetics

- BI 10773 was rapidly absorbed, reaching peak levels in 1.25 to 2.5 hours after single oral doses of 1 to 100 mg of BI 10773.
- Plasma concentration-time profiles showed a biphasic decline, i.e., with a rapid distribution phase and a slower elimination phase. The mean terminal elimination half-life ranged from 7.70 to 11.2 hours.
- Increases in BI 10773 exposure (AUC and C_{max}) were proportional to dose from 1 to 100 mg of BI 10773.
- Oral clearance was independent of dose and ranged from 139 to 167 mL/min in single-rising-dose part.
- The fraction of drug excreted unchanged in the urine ranged from 21.1% to 23.1% of the administered dose of BI 10773 in the single-rising-dose part.
- In the oGTT part, the systemic exposure and urinary excretion of BI 10773 were slightly higher than those observed at the same dose of BI 10773 in the single-rising-dose part.

Pharmacodynamics

- The urinary glucose excretion increased with BI 10773 dose compared with that with placebo. The maximum rate of the urinary glucose excretion increased with dose.
- Duration of effect on the urinary glucose excretion increased with BI 10773 dose compared with that with placebo.
- Plasma glucose levels in the single-rising-dose part were not changed with BI 10773 administration compared with that with placebo administration.

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Efficacy / clinical pharmacology results (continued)	• The increases in plasma glucose after an oGTT were slightly reduced by pre-treatment with 10 mg of BI 10773. • Under the controlled high fluid intake conditions in this trial, urine volumes were not greatly different among all treatment groups. The exposure in the Japanese subjects was slightly higher than that in the Caucasian subjects observed in the previous trial. On the other hand, the amount of urinary glucose excretion within 24 hours was comparable between the Japanese subjects and the Caucasian subjects. Therefore, the difference in exposure is not considered clinically relevant.
Safety results:	No deaths, serious adverse events, nor other significant adverse events were reported in this trial. During the treatment period, 9 adverse events of mild intensity including 3 drug-related events were reported by 8 of the 48 subjects. All the subjects had been recovered from the adverse events before the end-of-study examination without any treatment. No hypoglycaemia occurred during the trial. No subjects were withdrawn from the trial because of adverse events. Clinically significant values were not noted in the laboratory test results including renal function parameters during the treatment period. Clinically significant changes from the baseline values were not noted in vital signs or ECGs. In summary, there were no adverse events arousing an apprehension about further development of BI 10773 in this trial in the healthy Japanese subjects, and the safety data support the safety profile of BI 10773 obtained in the previous non-clinical and clinical studies.

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Conclusions:

After single oral administration, BI 10773 was rapidly absorbed and the plasma concentration-time profiles showed a biphasic decline. The pharmacokinetics of BI 10773 were dose-proportional. The urinary glucose excretion was enhanced even at the lowest dose of BI 10773 tested in this trial (1 mg) and increased with dose of BI 10773. Plasma glucose levels were not changed by a single oral administration of BI 10773.

Overall, BI 10773 was safe and well tolerated in the healthy Japanese male subjects.