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 Study Report**		
Name of finished product: Not applicable				
Name of active ingredient: BI 44847		**Page:**	**Number:**	
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Title of study:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses (2.5 mg to 1200 mg) of BI 44847 as powder in the bottle reconstituted with 0.2% natrosol solution administered to healthy male subjects. A randomised, placebo-controlled (within dose groups) and double-blinded trial
Investigator:	[redacted]
Study center:	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
Objectives:	To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 44847
Methodology:	Randomised, double-blind, placebo-controlled within dose groups, single rising dose (SRD), single centre
No. of subjects:	
planned:	entered: 72 SRD arm: 72 oral glucose tolerance test (OGTT) arm: 8
actual:	entered: 72 SRD arm: 72 OGTT arm: 8 Treatment A: BI 44847 entered: 54 treated: 53 analysed: 53 Treatment B: Placebo entered: 18 treated: 18 analysed: 18
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 50 years, with a Body Mass Index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 44847 as powder in the bottle (PIB)
dose:	as solution: 2.5 mg, 10 mg, 40 mg, 100 mg, and 200 mg as suspension: 400 mg, 800 mg, 1000 mg, and 1200 mg
mode of admin.:	Taken by mouth (p.o.) with 240 mL water, either in fasted state (SRD arm) or under OGTT conditions

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batch no.:	BI 44847, powder for oral solution 1000 mg: B061001164 BI 44847, powder for oral solution 400 mg: B061001185 BI 44847, powder for oral solution 100 mg: B061001186 BI 44847, powder for oral solution 20 mg: B061001195 Natrosol® solution 0.2%: B051000359 and B051000361
Duration of treatment:	Single dose
Reference therapy:	Placebo as PIB
dose:	—
mode of admin.:	Taken p.o. with 240 mL water, either in fasted state (SRD arm) or under OGTT conditions
batch no.:	Placebo, powder for oral solution 400 mg and 1000 mg: B061001105 Placebo, powder for oral solution 20 mg and 100 mg: B061001104 Natrosol solution 0.2%: B051000359 and B051000361
Criteria for evaluation:	
Efficacy:	Pharmacokinetic (PK) 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}, $CL_{R,t1-t2}$ Pharmacodynamic (PD) parameter: glucose in urine Biomarker: plasma glucose
Safety:	Tolerability, adverse events, 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 44847 was explored using a regression model. A 95% confidence interval for the slope was computed.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacodynamics and biomarker

Urinary glucose excretion (UGE) was increased at all doses of BI 44847 relative to placebo. The cumulative amount of glucose excreted in the 24 hours and 72 hours after dosing increased with dose from 2.5 to 1200 mg BI 44847. The maximum rate of UGE was not dose-dependent at doses of 40 mg BI 44847 and higher. This might indicate saturation of the SGLT-2 transporter.

Except for one outlier, urinary glucose excretion after treatment with 2.5 mg BI 44847 was similar to that following placebo. At doses of 10 to 200 mg, the pharmacodynamic effect of BI 44847 was characterised by rapid onset – the highest rate of UGE was observed in the urine collection interval of 0 to 2 hours – and a rapid decline. In contrast, the rate of UGE at doses of 400 to 1200 mg reached maximal levels in the urine collection interval of 4 to 6 hours and persisted for a longer duration of time.

For the 10 mg dose group, most of the UGE was observed within 6 hours after dosing. For the 40 to 1200 mg dose groups, most of the UGE was observed within 12 hours after dosing.

The glucosuric effect of BI 44847 was also observed under OGTT conditions. In fact, higher UGE was observed when 400 mg BI 44847 was administered under OGTT conditions than when the drug was given in the fasted state.

In both the SRD and the OGTT arms, no effect on plasma glucose concentration was observed after administration of single doses of BI 44847 to healthy male volunteers. No relevant changes compared to placebo were observed in either urine volume or urinary creatinine excretion.

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Safety results:

Pharmacokinetics

Single doses of BI 44847 were rapidly absorbed following oral administration to healthy volunteers. The t_{max} ranged from 0.342 to 0.517 hours. The gMean $t_{1/2}$ was 1.20 to 1.77 hours for doses of 2.5 to 200 mg and 3.63 to 6.19 hours for doses of 400 to 1200 mg. Due to a limitation in the sensitivity of detection in plasma with the lower dose groups, the latter range was considered more representative. The gMean clearance CL/F was high and ranged from 2920 to 9550 mL/min. Renal clearance ranged from 1 to 5% of the administered dose; its contribution to total clearance was considered negligible. The pharmacokinetics of 400 mg BI 44847 were not affected by administration of the drug under OGTT conditions.

In terms of dose proportionality, dose-normalised $AUC_{0-\infty}$, AUC_{0-8} and C_{max} showed an approximately proportional pattern until 400 mg and then a more than proportional increase. The reason for this non proportionality at doses above 400 mg is not known.

A total of 13 subjects (18.3%) experienced 17 AEs during this study. The overall frequency of subjects experiencing any AE during the treatment periods (excluding screening and post-treatment periods) was not higher with BI 44847 than with placebo (13.2% compared with 16.7% in the SRD arm, 33.3% compared with 50.0% in the OGTT arm). The most frequently reported AE was headache. All AEs were considered mild in intensity and all subjects recovered from the AEs.

Five subjects (7.0%) experienced 6 AEs which the investigator considered to be possibly related to the study drug, mainly diarrhoea. The overall frequency of subjects experiencing investigator-defined drug-related AEs was similar with BI 44847 (7.5%) and with placebo (5.6%).

No serious adverse events or deaths occurred during the study. There were no clinically relevant findings of the clinical laboratory evaluation, vital signs, or 12-lead ECG. Global tolerability was assessed as ‘good’ in 69 subjects and ‘satisfactory’ in one subject treated with 1200 mg BI 44847 and one subject treated with matching placebo.

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Conclusions:	Single doses of 2.5 to 1200 mg BI 44847 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 44847. In both the SRD and the OGTT arms, all doses demonstrated efficacy in increasing urinary glucose excretion without causing changes in urine volume, creatinine excretion, or plasma glucose. The duration and cumulative amount of urinary glucose excretion increased with dose. Administration of BI 44847 under OGTT conditions resulted in greater urinary glucose elimination than when the drug was administered in the fasted state. BI 44847 was rapidly absorbed and had a quick onset of action and a short elimination half-life. The pharmacokinetics of 400 mg BI 44847 were not affected by administration of the drug under OGTT conditions.