Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-023152-85	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 NOV 2011	**Trial No. / U No.:** 1245.58 / U11-2643-01	**Dates of trial:** 24 FEB 2011 – 03 MAY 2011	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of single dose BI 10773 co-administered with multiple doses of 600 mg gemfibrozil bid compared to single dose treatment of BI 10773 alone in healthy volunteers – a phase I, open-label, randomised, 2-way crossover trial
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine/Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	The objective of this trial was to investigate the relative bioavailability of a single dose of empagliflozin (BI 10773, 25 mg) when given alone compared with co-administration on the third day of a 5-day treatment with gemfibrozil (600 mg twice daily) in healthy volunteers.
Methodology:	This was an open-label, 2-way crossover trial with 2 treatments (A and B) and 2 treatment sequences (A_B and B_A).
No. of subjects:	
planned:	entered: 18 male and female subjects (at least 6 of each gender)
actual:	entered: 18 subjects (11 male and 7 female subjects) Treatment A (empagliflozin + gemfibrozil): treated and analysed (for primary endpoint): 18 subjects Treatment B (empagliflozin alone): treated and analysed (for primary endpoint): 18 subjects
Diagnosis and main criteria for inclusion:	Healthy male and female subjects at the age of 18 to 55 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.

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Test product 1:	Empagliflozin film-coated tablet
dose:	25 mg single dose
mode of admin.:	Oral administration with 240 mL of water
batch no.:	909473A
Test product 2:	Gemfibrozil film-coated tablet (Gevilon®)
dose:	600 mg twice daily
mode of admin.:	Oral administration with 240 mL of water
batch no.:	0939070
Duration of treatment:	Treatment A: Gemfibrozil was given twice daily for 5 days starting on Day -2 and empagliflozin was given as a single dose on Day 1, with gemfibrozil under steady-state conditions. Treatment B: Empagliflozin was given as a single dose on Day 1. A washout period of at least 7 days was required between drug administrations in the 2 treatments.
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic parameters were analysed as primary endpoints: $AUC_{0-\infty}$ and C_{max} for empagliflozin. The following pharmacokinetic parameter was assessed as secondary endpoints: AUC_{0-tz} for empagliflozin. In addition, the following pharmacokinetic parameters were assessed: t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F for empagliflozin and $C_{pre,N}$ for gemfibrozil.
Safety:	The evaluation of safety was based on physical examination, monitoring of vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests (clinical chemistry, urinalysis, haematology, and coagulation), monitoring of adverse events, and assessment of overall tolerability.

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Statistical methods:

Point estimators (geometric means) of the geometric mean (gMean) intrasubject ratios for $AUC_{0-\infty}$, C_{max}, and AUC_{0-tz} and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period', and 'treatment'. Confidence intervals were based on the t-distribution.

Descriptive statistics were calculated for all pharmacokinetic endpoints and the safety data.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

All 18 entered subjects completed the trial according to the clinical trial protocol. The trial population consisted of healthy white male and female subjects. The mean age was 35.1 years, ranging from 20 to 55 years, and the mean BMI was 23.47 kg/m^2, ranging from 20.3 to 28.4 kg/m^2.

Following administration of a single oral dose of empagliflozin in combination with multiple oral doses of gemfibrozil (treatment A) or alone (treatment B), plasma concentrations of empagliflozin reached peak concentrations rapidly (3.00 h and 2.59 h after drug administration, respectively) and then declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. Empagliflozin exposure was higher when a single oral dose of empagliflozin (25 mg) was given together with multiple oral doses of gemfibrozil (600 mg twice daily) than after administration of empagliflozin alone ($AUC_{0-\infty}$: 7630 nmol·h/L compared with 4770 nmol·h/L; C_{max}: 713 nmol/L compared with 610 nmol/L). The terminal elimination half-life of empagliflozin was similar with and without co-administration with gemfibrozil (13.6 h and 13.3 h, respectively). However, oral clearance and volume of distribution were somewhat lower during the combined treatment compared with empagliflozin treatment alone (CL/F: 127 mL/min compared with 199 ml/min; V_z/F: 147 L compared with 224 L).

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Clinical pharmacology results (continued):

The relative bioavailability of empagliflozin when given together with gemfibrozil (treatment A) compared with empagliflozin given alone (treatment B) was determined. The gMean ratios and 2-sided 90% CIs for empagliflozin $AUC_{0-\infty}$ and C_{max} in treatments A and B were compared using the standard bioequivalence criteria of 80% to 125%. Although the peak concentrations (C_{max}) of empagliflozin were numerically slightly higher during the combined treatment than during treatment with empagliflozin, the gMean ratio of 115.00% and the corresponding 90% CI of 106.15% to 124.59 % were within the standard bioequivalence range. The overall exposure ($AUC_{0-\infty}$) of empagliflozin was roughly 60% higher during the combined treatment than during treatment with empagliflozin alone with a gMean ratio (90% CIs) of 158.50% (151.77 to 165.53%). Intraindividual variability was low in the case of both $AUC_{0-\infty}$ and C_{max} (intraindividual gCV was 7.5% for $AUC_{0-\infty}$ and 13.8% for C_{max}).

Safety results:

Each of the 18 treated subjects received a total dose of 50 mg empagliflozin (a single 25 mg dose each in treatment A and treatment B) and a total dose of 6000 mg gemfibrozil (600 mg twice daily for 5 days during treatment A) during the course of the trial as planned in the clinical trial protocol.

No serious adverse events and no other significant adverse events according to ICH E3 were reported in this trial. In this trial, a total of 12 subjects (66.7%) reported at least 1 adverse event in at least 1 of the 3 treatment periods 'gemfibrozil' (starting with the first gemfibrozil administration in treatment A), 'gemfibrozil + empagliflozin' (starting with the empagliflozin administration in treatment A), and 'empagliflozin' (starting with the empagliflozin administration in treatment B). The frequency of subjects with adverse events was highest during the treatment period 'empagliflozin' (8 subjects, 44.4%), followed by 'gemfibrozil' (6 subjects, 33.3%) and 'gemfibrozil + empagliflozin' (3 subjects, 16.7%). The investigator classified 1 adverse event (dyspepsia of mild intensity), which was reported during the treatment period 'gemfibrozil', as related to gemfibrozil. All other adverse events were judged as not drug-related. All adverse events were of mild or moderate intensity.

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Safety results (continued):

The most frequently reported adverse events overall at the system organ class level were nervous system disorders, which were experienced by a total of 7 subjects (38.9%). The most frequent on-treatment adverse event overall by preferred term was headache (5 subjects, 27.8%), followed by dizziness (2 subjects, 11.1%) and haematoma (2 subjects, 11.1%).

In this trial, there were no clinically relevant findings reported as an adverse event regarding laboratory measurements, ECG recordings and vital sign measurements. The investigator rated the overall tolerability during treatment A (combined treatment) as 'good' for all 18 subjects. During treatment B (empagliflozin alone), the overall tolerability was rated as 'good' for 17 subjects and as 'satisfactory' for 1 subject.

Conclusions:

Co-administration of gemfibrozil with empagliflozin resulted in a moderate increase in the overall exposure of empagliflozin. The gMean ratio for $AUC_{0-\infty}$ was 158.50% and the corresponding 90% CI of 151.77% to 165.53% was outside the standard bioequivalence boundaries. The peak concentrations (C_{max}) of empagliflozin were numerically slightly higher during the combined treatment than during treatment with empagliflozin alone, but the gMean ratio of 115.00% and the corresponding 90% CI of 106.15% to 124.59 % were within the standard bioequivalence boundaries of 80% to 125%. The observed increase in the overall exposure of empagliflozin was less than 2-fold and was not considered to be clinically relevant. Therefore, no dosage adjustment of empagliflozin is recommended when administered concomitantly with gemfibrozil.

Overall, administration of a single dose of empagliflozin alone or in combination with multiple doses of gemfibrozil was well tolerated by the healthy male and female subjects in this trial.

Trial Synopsis – Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended table provides results of a secondary endpoint as summarized below.

Results for	**presented in**
$AUC_{0\text{-}tz}$	Table 15.5.1.3: 2

Table 15.5.1.3: 2 Adjusted by-treatment geometric means and relative bioavailability
comparison BI+Gemfi : BI10773, PK set
AUClast [nmol*h/L] for BI 10773 (PLASMA)

BI+Gemfi N	BI+Gemfi gMean	BI10773 N	BI10773 gMean	Ratio BI+Gemfi : BI10773 [%]	gSE	90% Confidence interval [%]		Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
18	7350.84	18	4643.81	158.29	1.03	151.41	165.49	7.7	1.0000