Boehringer Ingelheim

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.

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		**EudraCT No.:** 2010-023680-18	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 NOV 2011	**Trial No. / U No.:** 1245.63 / U11-2575-01	**Dates of trial:** 22 FEB 2011 – 06 APR 2011	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of BI 10773 and simvastatin after single and combined administration - an open-label, randomised, crossover trial in healthy subjects
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany
Publication (reference):	Data from this trial have not been published
Clinical phase:	I
Objectives:	To study the drug-drug interaction potential between empagliflozin and simvastatin
Methodology:	This was an open-label, randomised, single dose, three-way crossover trial with 3 treatment periods separated by at least 7 days between drug administrations
No. of subjects:	
planned:	entered: 18
actual:	Treatment A (25 mg empagliflozin): entered: 18 treated: 18 analysed (for primary endpoint): 18 Treatment B (40 mg simvastatin): entered: 18 treated: 17 analysed (for primary endpoint): 17 Treatment C (25 mg empagliflozin together with 40 mg simvastatin): entered: 18 treated: 18 analysed (for primary endpoint): 18
Diagnosis and main criteria for inclusion:	Healthy volunteers, male and female, age 18 to 50 years inclusive, body mass index 18.5 to 29.9 kg/m^2 inclusive
Trial product 1:	Empagliflozin (BI 10773) film-coated tablet
dose:	25 mg, single dose
mode of admin.:	Oral
batch no.:	909473A

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Trial product 2:	Simvastatin (Zocor forte®) film-coated tablet
dose:	40 mg, single dose
mode of admin.:	Oral
batch no.:	302431
Duration of treatment:	Single dose in each treatment period separated by a wash-out phase of at least 7 days between administrations
Criteria for evaluation:	
Clinical pharmacology:	For empagliflozin, simvastatin, and simvastatin acid (active metabolite) Primary endpoints: $AUC_{0-\infty}$ and C_{max} Secondary endpoints: AUC_{0-tz}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and V_z/F
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), laboratory tests, adverse events (AEs), and global tolerability assessment
Statistical methods:	Point estimators of the intra-subject ratios (geometric mean ratio; GMR) of $AUC_{0-\infty}$ and C_{max} of empagliflozin, simvastatin, and simvastatin acid and their two-sided 90% confidence intervals (CIs) were calculated. The statistical model was analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Confidence intervals were based on the residual error from ANOVA. Descriptive statistics for all pharmacokinetic parameters and for certain safety measurements were calculated.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Of the 18 healthy subjects (12 males and 6 females) entered, 17 completed all 3 treatments as planned, while 1 prematurely discontinued after the second treatment period due to an adverse event (purulent cyst in the right sinus maxillaris). Consequently, 18 subjects received Treatments A (empagliflozin 25 mg) and C (combined) while 17 received Treatment B (simvastatin 40 mg). Seventeen subjects were white and 1 was black/African American. They had a mean (range) age of 35.9 (20-50) years and body mass index of 24.37 (19.4-29.4) kg/m^2.

Summary of the primary pharmacokinetic endpoints and t_{max} for empagliflozin, simvastatin, and simvastatin acid are provided in the tables below. No major difference in $AUC_{0-\infty}$, C_{max}, or t_{max} was observed when comparing the single and combined administration for any of the 3 analytes.

Parameter **Mean (%CV)**	**Empagliflozin**	
	Empagliflozin 25 mg (N=18)	Empagliflozin 25 mg + simvastatin 40 mg (N=18)
$AUC_{0-\infty}$ [nmol*h/L]	5680 (20.8)	5800 (22.7)
C_{max} [nmol/L]	806 (30.0)	876 (27.2)
t_{max} [h]	1.39 (51.2)	1.25 (50.7)

Parameter **Mean (%CV)**	**Simvastatin**		**Simvastatin acid**	
	Simvastatin 40 mg (N=17)	Empagliflozin 25 mg + simvastatin 40 mg (N=18)	Simvastatin 40 mg (N=17)	Empagliflozin 25 mg + simvastatin 40 mg (N=18)
$AUC_{0-\infty}$ [ng*h/mL]	40.4 (57.2)	40.2 (54.6)	21.7 (71.9)	22.7 (77.0)
C_{max} [ng/mL]	9.93 (67.8)	9.40 (62.2)	1.90 (68.2)	1.84 (73.1)
t_{max} [h]	1.32 (103)	1.13 (57.1)	4.29 (42.8)	4.53 (33.6)

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Results of the relative bioavailability analysis are summarised in the table below. The adjusted GMRs of $AUC_{0-\infty}$ and C_{max} for empagliflozin, simvastatin, and simvastatin acid were all close to 100% and their respective 90% CIs were within the standard bioequivalence range of 80-125% except for the upper limit of $AUC_{0-\infty}$ and the lower limit of C_{max} for simvastatin. However, simvastatin is a prodrug and is hydrolysed to its active β-hydroxyacid form, simvastatin acid, after administration. As the 90% CIs of the active moiety are within the standard bioequivalence range, it can be concluded that the minor deviations observed in the case of the parent levels are not clinically relevant.

Analyte	Parameter	Adjusted GMR of single to combined administration [%]	90% CI	Intra-subject gCV [%]
Empagliflozin	$AUC_{0-\infty}$	102.05	98.90-105.29	5.4
	C_{max}	109.49	96.91-123.69	21.1
Simvastatin	$AUC_{0-\infty}$	101.26	80.06-128.07	40.4
	C_{max}	97.18	76.30-123.77	41.7
Simvastatin acid	$AUC_{0-\infty}$	104.87	90.09-122.07	25.5
	C_{max}	97.27	84.90-111.44	22.7

Safety results:

After 18 male and female subjects had received 25 mg empagliflozin and 40 mg simvastatin in single or combined administration, 12 (66.7%) reported a total of 17 AEs. Six subjects (33.3%) reported altogether 7 AEs in the empagliflozin treatment period, 4 (23.5%) reported 4 AEs in the simvastatin treatment period, and 5 (27.8%) reported 6 AEs in the combined treatment period. The most common AE was mild headache, experienced by 7 subjects in total. There was 1 severe AE (purulent cyst in the right sinus maxillaris) that caused trial discontinuation of the subject. No investigator-defined drug-related AE, serious AE, or clinically relevant finding in laboratory evaluation, physical examination, vital signs, or 12-lead ECG was reported.

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Conclusions: Simvastatin co-administration had no effect on the pharmacokinetics of empagliflozin, as determined by the standard bioequivalence boundaries. Empagliflozin co-administration had no clinically relevant effect on pharmacokinetics of simvastatin and no effect on the kinetics of its active metabolite, simvastatin acid. The results demonstrate that there is no drug-drug interaction between empagliflozin and simvastatin. Furthermore, combined single dose administration of empagliflozin and simvastatin was safe and well tolerated.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide complete results of additional secondary endpoints, as summarised below.

Results for	**presented in**
Adjusted by-treatment means and relative bioavailability comparison BI10773+Sim to BI10773, AUC_{last} [ng*h/mL] for BI10773	Table 15.5.1.3: 2
Adjusted by-treatment means and relative bioavailability comparison BI10773+Sim to simvastatin, AUC_{last} [ng*h/mL] for simvastatin	Table 15.5.2.3: 2

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

BI10773+Sim N	BI10773+Sim gMean	BI10773 N	BI10773 gMean	Ratio BI10773+Sim : BI10773 [%]	gSE	90% Confidence interval [%]		Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
18	5619.60	18	5481.31	102.52	1.02	99.10	106.06	5.8	0.0000

Table 15.5.2.3: 2 Adjusted by-treatment geometric means and relative bioavailability comparison BI10773+Sim : Simvastatin, PK analysis set AUClast [ng*h/mL] for SIMVASTATIN (PLASMA)

BI10773+Sim N	BI10773+Sim gMean	Simvastatin N	Simvastatin gMean	Ratio BI10773+Sim : Simvastatin [%]	gSE	90% Confidence interval [%]		Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
						[%]	[%]		
18	32.57	17	31.82	102.34	1.15	80.39	130.29	41.7	0.0834