Boehringer Ingelheim

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		**EudraCT No.:** 2010-022717-25	
Name of active ingredients: Empagliflozin (BI 10773), ramipril		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1245.45 / U11-2593-01	**Dates of trial:** 20 JAN 2011 – 21 MAR 2011	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of multiple oral doses of BI 10773 (25 mg) and ramipril (5 mg) administered together compared to multiple oral doses of BI 10773 (25 mg) alone and ramipril (5 mg) alone in healthy male and female volunteers (an open-label, randomised, three-way crossover, clinical phase I study)
Principal Investigator	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre Biberach, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objective was to investigate whether empagliflozin (BI 10773) affects the pharmacokinetics of ramipril and whether ramipril affects the pharmacokinetics of empagliflozin.
Methodology:	This was an open-label, randomised, multiple-dose, 3-way crossover study.
No. of subjects:	
planned:	entered: 24
actual:	entered: 23 Treatment A: Empagliflozin alone treated: 22 analysed (for primary endpoints): 22 Treatment B: Ramipril alone treated: 22 analysed (for primary endpoints): 22 Treatment C: Empagliflozin and ramipril in combination treated: 23 analysed (for primary endpoints): 23
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers at the age of 18 to 55 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included in the study.
Investigational product 1:	Empagliflozin tablet
dose:	25 mg once daily
mode of admin.:	Oral
batch no.:	909473A

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022717-25	
Name of active ingredients: Empagliflozin (BI 10773), ramipril		**Page:** 2 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1245.45 / U11-2593-01	**Dates of trial:** 20 JAN 2011 – 21 MAR 2011	**Date of revision:** Not applicable

Investigational product 2:	Ramipril tablet (Delix®)
dose:	2.5 mg single dose (Day 1), 5 mg once daily (given as two 2.5 mg tablets on Days 2 to 5)
mode of admin.:	Oral
batch no.:	H488 (Sanofi-Aventis)
Duration of treatments:	In Treatment A, empagliflozin 25 mg once daily was administered for 5 days. In Treatment B, a single dose of ramipril 2.5 mg was administered on Day 1, while ramipril 5 mg once daily was administered on Days 2 to 5. In Treatment C, empagliflozin 25 mg once daily and ramipril (2.5 mg on Day 1, 5 mg once daily on Days 2 to 5) were administered together for 5 days. The last drug administration of the preceding treatment and the first drug administration of the following treatment were separated by a washout period of at least 7 days.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters of empagliflozin, ramipril, and ramiprilat (active metabolite of ramipril): Primary endpoints: $AUC_{\tau,ss}$ and $C_{max,ss}$ Secondary endpoints: $C_{pre,N}$, $t_{max,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, CL/F_{ss}, V_z/F_{ss}
Safety:	Physical examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests (haematology, clinical chemistry, coagulation, and urinalysis), analysis of adverse events (AE), and an assessment of tolerability by the investigator
Statistical methods:	The geometric mean point estimates for the geometric mean intrasubject ratios of $AUC_{\tau,ss}$ (Test) to $AUC_{\tau,ss}$ (Reference) and of $C_{max,ss}$ (Test) to $C_{max,ss}$ (Reference) and their 2-sided 90% confidence intervals (CIs) were calculated. Empagliflozin coadministered with ramipril was regarded as the Test treatment; empagliflozin alone or ramipril alone was regarded as the Reference treatment. The statistical model was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. The effect 'subjects within sequences' was considered as random whereas the other effects were considered as fixed. Steady-state trough concentrations of empagliflozin and ramipril were investigated by a

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022717-25	
Name of active ingredients: Empagliflozin (BI 10773), ramipril		**Page:** 3 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1245.45 / U11-2593-01	**Dates of trial:** 20 JAN 2011 – 21 MAR 2011	**Date of revision:** Not applicable

repeated measures ANOVA model on the logarithmic scale including 'time' as a repeated effect and 'subject' as a random effect. Descriptive statistics for $AUC_{\tau,ss}$ and $C_{max,ss}$, other pharmacokinetic parameters, and safety characteristics were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

The study population consisted of 23 healthy subjects, 15 female and 8 male. All subjects were white. The mean age was 38.0 years, ranging from 21 to 52 years, and the mean BMI was 24.32 kg/m^2. Twenty-two subjects completed all 3 treatment periods whereas 1 subject discontinued the study after the first treatment period (empagliflozin and ramipril) as she needed thrombosis prophylaxis because of a ligament rupture in the knee during the screening period.

Relative bioavailabilities of empagliflozin, ramipril, and ramiprilat were estimated on the basis of geometric mean ratios (GMR) of Test/Reference of $AUC_{\tau,ss}$ and $C_{max,ss}$. The GMRs for all 3 analytes were close to unity and their respective 90% CIs were all within the 80 to 125% acceptance range for bioequivalence. Intraindividual variability was generally low in case of all 3 analytes. The following table summarises the results of the relative bioavailability comparisons.

Analyte Parameter	Test[1] geometric mean	Reference[2] geometric mean	Adjusted GMR [%]	Two-sided 90% CI Lower limit [%]	Two-sided 90% CI Upper limit [%]	gCV[3] [%]
Empagliflozin						
$AUC_{\tau,ss}$ [nmol·h/L]	5614.20	5814.77	96.55	93.05	100.18	7.1
$C_{max,ss}$ [nmol/L]	898.58	860.14	104.47	97.65	111.77	13.1
Ramipril						
$AUC_{\tau,ss}$ [ng·h/mL]	7.19	6.65	108.14	100.51	116.35	14.0
$C_{max,ss}$ [ng/mL]	8.84	8.53	103.61	89.73	119.64	28.0
Ramiprilat						
$AUC_{\tau,ss}$ [ng·h/mL]	84.94	86.09	98.67	96.00	101.42	5.2
$C_{max,ss}$ [ng/mL]	10.46	10.65	98.29	92.67	104.25	11.3

[1]Test: empagliflozin and ramipril (N=23)
[2]Reference: ramipril alone (N=22) or empagliflozin alone (N=22)
[3]Intraindividual geometric coefficient of variation

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022717-25	
Name of active ingredients: Empagliflozin (BI 10773), ramipril		**Page:** 4 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 NOV 2011	**Trial No. / U No.:** 1245.45 / U11-2593-01	**Dates of trial:** 20 JAN 2011 – 21 MAR 2011	**Date of revision:** Not applicable

Safety results:

Twenty-two subjects were administered a total dose of 250 mg empagliflozin and a total dose of 45 mg ramipril during the trial as planned. The subject who discontinued after the first treatment period received a total dose of 125 mg empagliflozin and 22.5 mg ramipril.

No deaths, other SAEs, or other significant AEs (ICH E3 definition) occurred in this study. Eleven subjects (47.8%) reported at least 1 AE during the treatment phase of the study: 3 subjects (13.6%) during treatment with empagliflozin alone, 6 subjects (27.3%) during treatment with ramipril alone, and 5 subjects (21.7%) during the combined treatment. The most frequently reported AE overall was headache (4 subjects, 17.4%) followed by nausea (2 subjects, 8.7%). Headache was reported by 3 subjects (13.6%) under ramipril treatment and by 1 subject (4.5%) under empagliflozin treatment. Nausea in both cases occurred in the treatment period with empagliflozin and ramipril and was judged related to trial medication. All AEs were of mild or moderate intensity with 1 exception: hyperventilation of severe intensity in the treatment period with ramipril. The event was judged unrelated to trial medication. Two subjects (8.7%) reported AEs that were considered drug-related: 1 subject reported fatigue and upper abdominal pain under empagliflozin as well as nausea under the combined treatment; the other subject also reported nausea under the combined treatment.

The clinical laboratory evaluation did not reveal any clinically relevant changes in laboratory parameters and there were no findings with respect to ECG recordings. The treatment ramipril alone and the combined treatment resulted in maximal mean reductions from baseline in SBP/DBP of -7.4/-4.1 mmHg and -10.7/-5.3 mmHg, respectively. The investigator assessed the overall tolerability of the treatments investigated as good in all subjects.

Conclusions:

Ramipril coadministration had no clinically relevant effect on the pharmacokinetics of empagliflozin, as determined by the standard bioequivalence boundaries of 80 to 125%. Similarly, empagliflozin coadministration had no clinically relevant effect on the pharmacokinetics of ramipril and its active metabolite, ramiprilat, as determined by the standard bioequivalence boundaries. The results demonstrate that there is no drug-drug interaction between empagliflozin and ramipril.

Administration of multiple doses of empagliflozin alone or in combination with ramipril was safe and well tolerated by the healthy male and female subjects.