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.:** 2012-000971-17	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 DEC 2012	**Trial No. / U No.:** 1245.83 / U12-2462-01	**Dates of trial:** 02 JUL 2012 – 07 AUG 2012	**Date of revision:** Not applicable

Title of trial:	A randomised, open-label, three-way crossover trial to investigate the effect of rifampicin and probenecid on empagliflozin pharmacokinetics in healthy male and female subjects
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre/Dept. of Translational Medicine, Birkendorfer Strasse 65, Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objectives:	The primary objective was to investigate the effect of a single dose of rifampicin, a model organic anion-transporting polypeptide 1B1 (OATP1B1) inhibitor, and of multiple doses of probenecid, a model organic anion transporter 3 (OAT3) inhibitor, on the single dose pharmacokinetics of empagliflozin, by investigating the relative bioavailability of empagliflozin after concomitant administration with the above medications compared with administration of empagliflozin alone.
Methodology:	The study was conducted according to a randomised, open-label, three-way crossover design with 3 treatments (A, B, C) and 6 treatment sequences (A-B-C, B-C-A, C-A-B, A-C-B, B-A-C, or C-B-A). The reference treatment (treatment A) was a single dose of 10 mg empagliflozin. The test treatments were either a single dose of 10 mg empagliflozin combined with a single dose of 600 mg rifampicin (treatment B) or a single dose of 10 mg empagliflozin in the morning of Day 1 combined with 500 mg of probenecid given twice daily for 4 days from Day -1 to Day 3 (treatment C). There were washout periods of at least 7 days between each dose of empagliflozin.

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No. of subjects:	
Planned:	Entered: 18
Actual:	Entered: 18 Treatment A (empagliflozin 10 mg, single dose): Treated: 18, analysed (for primary endpoints): 18 Treatment B (empagliflozin 10 mg + rifampicin 600 mg, single doses): Treated: 18, analysed (for primary endpoints): 18 Treatment C (empagliflozin 10 mg, single dose on Day 1 + probenecid 500 mg twice daily for 4 days [Day -1 to Day 3]): Treated: 16, analysed (for primary endpoints): 16
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers at the age of 18 to 50 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2
Trial product 1:	Empagliflozin film-coated tablets
Dose:	1 film-coated tablet of 10 mg as single dose
Mode of admin.:	Oral
Batch no.:	PR12/10244
Trial product 2:	Rifampicin film-coated tablets
Dose:	1 film-coated tablet of 600 mg as single dose
Mode of admin.:	Oral
Batch no.:	027121 (Riemser Arzneimittel AG)
Trial product 3:	Probenecid tablets
Dose:	1 tablet of 500 mg twice daily
Mode of admin.:	Oral
Batch no.:	1117351 (Biokanol Pharma GmbH)

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Duration of treatment:	Treatment A: 10 mg empagliflozin, single dose Treatment B: 10 mg empagliflozin + 600 mg rifampicin, single doses Treatment C: 10 mg empagliflozin, single dose in the morning of Day 1 combined with 500 mg probenecid twice daily for 4 days (Day -1 to Day 3) There were washout periods of at least 7 days between each dose of empagliflozin.
Criteria for evaluation:	
Clinical pharmacology:	Primary pharmacokinetic (PK) endpoints: $AUC_{0-\infty}$ and C_{max} of empagliflozin Secondary PK endpoint: AUC_{0-tz} of empagliflozin
Safety:	The safety evaluation was based on the analysis of adverse events, clinical and laboratory tests (haematology, clinical chemistry, and urinalysis), vital signs (blood pressure, pulse rate), physical examinations, and 12-lead resting electrocardiograms (ECG).
Statistical methods:	Point estimators (geometric means) of the intra-subject ratios of $AUC_{0-\infty}$, C_{max}, and AUC_{0-tz} of empagliflozin 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 within sequences', 'period', and 'treatment'. Descriptive statistics were calculated for all plasma concentrations, pharmacokinetic parameters, urinary glucose excretion, and safety criteria.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	A total of 18 healthy White subjects, 10 males and 8 females, participated in the study. Their mean age was 32.7 years and their mean body mass index was 23.03 kg/m^2. Sixteen subjects received all 3 treatments A, B, and C and 2 subjects received treatments A and B only. None of the subjects reported any concomitant diagnoses at baseline. Relative bioavailabilities of empagliflozin were determined after co-administration with rifampicin or probenecid compared with the administration of empagliflozin alone.

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The geometric mean ratios (GMRs) and 2-sided 90% CIs for $AUC_{0-\infty}$, C_{max}, and AUC_{0-tz} with and without co-administration were compared using the standard bioequivalence method. Co-administration with rifampicin led to an increase in empagliflozin $AUC_{0-\infty}$ by 35.20% and C_{max} by 75.14% compared with empagliflozin alone. Co-administration with probenecid led to an increase in empagliflozin $AUC_{0-\infty}$ by 53.47% and C_{max} by 25.60% compared with empagliflozin alone. Intra-individual variability between the treatments was low for both $AUC_{0-\infty}$ and C_{max}.

The following table summarises the geometric mean ratios and 2-sided 90% CIs for $AUC_{0-\infty}$ and C_{max} of empagliflozin.

Treatment		Parameter	GMR	2-sided 90% CI	
Test (T)	Reference (R)		T/R [%]	Lower limit [%]	Upper limit [%]
Empagliflozin + rifampicin (treatment B)	Empagliflozin (treatment A)	$AUC_{0-\infty}$	135.20	129.58	141.06
		C_{max}	175.14	160.14	191.56
Empagliflozin + probenecid (treatment C)	Empagliflozin (treatment A)	$AUC_{0-\infty}$	153.47	146.41	160.88
		C_{max}	125.60	113.67	138.78

The increases in empagliflozin AUC_{0-tz} were 36.42% for co-administration with rifampicin and 53.61% for co-administration with probenecid.

Safety results:

Overall, 18 subjects were administered trial medication in this study. Sixteen subjects received all 3 treatments A, B, and C and thus total doses of 30 mg empagliflozin, 600 mg rifampicin, and 4000 mg probenecid. Two subjects received treatments A and B only because they discontinued the trial prematurely due to personal reasons; they received total doses of 20 mg empagliflozin and 600 mg rifampicin.

Thirteen out of 18 subjects (72.2%) reported at least 1 AE during the treatment periods of the trial: 7 subjects (38.9%) during treatment with empagliflozin alone, 9 subjects (50.0%) during combined treatment with empagliflozin and rifampicin, 6 subjects (37.5%) during combined treatment with empagliflozin and probenecid, and 2 subjects (12.5%) during treatment with probenecid alone.

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	The most frequently reported AEs overall were headache, nausea, and vomiting, experienced by 38.9%, 33.3 %, and 16.7% of the subjects, respectively. These AEs occurred in all empagliflozin treatment groups, whether empagliflozin was administered alone or in combination with rifampicin or probenecid. In the empagliflozin plus rifampicin treatment group dizziness was reported by 2 subjects (11.1%). All other AEs were experienced by 1 subject only. Ten subjects (55.6%) experienced a total of 24 AEs (mainly headache, nausea, and vomiting) that were assessed as drug-related by the investigator. The incidence of drug-related AEs was highest in the empagliflozin plus rifampicin treatment group. All AEs were of mild or moderate intensity. Two subjects required therapy for headache, nausea, or sciatica. No SAEs, no other significant AEs (according to ICH E3), and no AEs leading to discontinuation occurred in this trial. All subjects recovered from their AEs during the course of this trial. There were no notable findings with regard to the clinical laboratory evaluation, vital signs, and ECG recordings.
Conclusions:	Co-administration of rifampicin increased empagliflozin $AUC_{0-\infty}$ by approximately 35% and C_{max} by 75%. The corresponding increases caused by co-administration of probenecid were approximately 53% and 26%. The observed increases in the overall exposure of empagliflozin are not considered to be clinically relevant. Therefore, no dosage adjustment of empagliflozin is recommended when administered concomitantly with rifampicin or probenecid. Overall, a single dose of 10 mg empagliflozin was well tolerated when administered either alone or in combination with a single dose of 600 mg rifampicin, or with twice daily doses of 500 mg probenecid for 4 days to healthy male and female subjects.