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.:** 2010-023170-40	
Name of active ingredient: Empagliflozin		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 15 NOV 2011	**Trial No. / U No.:** 1245.40 / U11-2644-01	**Dates of trial:** 04 MAR 2011 –18 APR 2011	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of a single oral dose of digoxin (0.5 mg) when administered alone or in combination with multiple oral doses of BI 10773 (25 mg qd) in healthy male and female volunteers (an open-label, randomised, two-way crossover study)
Principal Investigator:	[redacted]
Trial site:	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:	The primary objective was to evaluate the effect of multiple doses of empagliflozin on the single dose pharmacokinetics of digoxin, a model P-gp substrate, by investigating the relative bioavailability of digoxin after concomitant administration of a single dose of digoxin with multiple oral doses of empagliflozin compared with administration of digoxin alone.
Methodology:	This was an open-label, randomised, two-way crossover trial. The reference treatment (Treatment A) was a single dose of 0.5 mg digoxin on Day 1. The test treatment (Treatment B) was 25 mg empagliflozin once daily (q.d.) on Days 1 to 8 combined with a single dose of 0.5 mg digoxin on Day 5. There was a washout period of at least 14 days between each dose of digoxin.
No. of subjects:	
planned:	Entered: 20
actual:	Entered: 20 Treatment A (Digoxin 0.5 mg): Entered: 20 treated: 20 analysed (for primary endpoint): 20 Treatment B (Empagliflozin 25 mg q.d. + digoxin 0.5 mg): Entered: 20 treated: 20 analysed (for primary endpoint): 19

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Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age 18 to 50 years, body mass index 18.5 to 29.9 kg/m^2
Trial product 1:	Empagliflozin 25 mg film-coated tablet
dose:	25 mg q.d.
mode of admin.:	Oral administration with 240 mL water
batch no.:	909473A
Trial product 2:	Digoxin 0.25 mg tablet
dose:	0.5 mg (single dose)
mode of admin.:	Oral administration with 240 mL water after an overnight fast of at least 10 h
batch no.:	1001
Duration of treatment:	Empagliflozin: 8 days Digoxin: 2 single doses (wash-out period of at least 14 days between each dose)
Criteria for evaluation:	
Pharmacokinetics:	*Primary endpoints:* $AUC_{0-\infty}$ and C_{max} of digoxin *Secondary endpoint:* AUC_{0-tz} of digoxin *Other endpoints:* $\%AUC_{tz-\infty}$, t_{max}, λ_z, $t_{½}$, MRT_{po}, CL/F, V_z/F, $Ae_{(cum)t1-t2}$, $fe_{(cum)t1-t2}$, and $CL_{R,0-24}$ of digoxin; $C_{pre,N}$ of empagliflozin
Safety:	Adverse events, vital signs (blood pressure, pulse rate), electrocardiogram (ECG), laboratory tests, physical examination, and assessment of tolerability
Statistical methods:	Point estimators of the geometric mean intra-subject ratios of $AUC_{0-\infty}$, C_{max}, $CL_{R,0-24}$, and AUC_{0-tz} of digoxin and their 2-sided 90% confidence intervals 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 primary and secondary endpoints and safety criteria.

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SUMMARY – CONCLUSIONS:

Pharmacokinetics results:

Twenty healthy volunteers were entered and treated in this trial – 11 male subjects and 9 female subjects. The mean (range) age and body mass index were 34.3 (20 to 50) years and 24.09 (20.2 to 29.4) kg/m^2. No subjects reported relevant concomitant diagnoses at baseline. Concomitant therapies, primarily oral contraceptives, were reported in 3 subjects, but these were not considered relevant. All subjects completed the trial according to the protocol.

Digoxin exposure was similar when 0.5 mg digoxin was given with 25 mg empagliflozin q.d. at steady state (mean $AUC_{0-\infty}$: 41.2 ng·h/mL, CV 25.9%; mean C_{max}: 2.36 ng/mL, CV 31.7%) and when digoxin was given alone (mean $AUC_{0-\infty}$: 38.7 ng·h/mL, CV 23.7%; mean C_{max}: 2.14 ng/mL, CV 40.3%).

There were no major differences in PK parameters of digoxin given with and without empagliflozin. The mean AUC_{0-tz} of digoxin was 29.2 ng·h/mL (CV 23.5%) when given with empagliflozin and 25.5 ng·h/mL (CV 23.5%) when given alone. The terminal elimination half-life (mean $t_{½}$: 55.4 h vs 68.7 h), the apparent plasma clearance (mean CL/F: 215 mL/min vs 226 mL/min), and the apparent volume of distribution (mean V_z/F: 1000 L vs 1270 L) of digoxin after a single oral dose were similar with and without empagliflozin.

No major differences in renal excretion of digoxin between the 2 treatments were observed. The mean fraction of digoxin excreted in urine (fe_{0-96}) was 40.1% of the dose when digoxin was given with empagliflozin and 40.6% when digoxin was given alone. The renal clearance of digoxin was also similar with and without empagliflozin (mean $CL_{R,0-24}$: 139 mL/min vs 153 mL/min).

The geometric mean ratio (GMR) of digoxin $AUC_{0-\infty}$ with and without empagliflozin was 106.11% and the 90% confidence interval (CI) was 96.71% to 116.41%, within the standard bioequivalence range of 80% to 125%. The GMR of digoxin C_{max} was 113.94% and the 90% CI was 99.33% to 130.70%, outside the standard bioequivalence range. Intraindividual variability for both $AUC_{0-\infty}$ and C_{max} was low.

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Safety results:	Each of the 20 subjects treated in this trial received 8 doses of 25 mg empagliflozin and 2 doses of 0.5 mg digoxin. Treatment-emergent adverse events were reported in 3 of 20 subjects after administration of digoxin alone. Mild headache and moderate fatigue were reported in one subject and moderate fatigue was reported in another subject, and severe influenza-like illness was reported in the third subject. The investigator considered headache and fatigue in both subjects related to the study medication. All subjects recovered from the adverse events and no adverse events lead to discontinuation of the trial drug. No adverse events were reported during treatment with empagliflozin and digoxin. No serious or other significant adverse events were reported. Global tolerability was good in all subjects, and there were no significant findings in clinical laboratory values, vital signs, or ECG.
Conclusions:	Co-administration of empagliflozin with digoxin had no significant effect on the overall exposure of digoxin as determined by standard bioequivalence boundaries. Empagliflozin had a slight effect on the peak levels of digoxin. The combination of empagliflozin and digoxin was well tolerated. These results demonstrate that no dose adjustment of digoxin is required when empagliflozin is prescribed concomitantly in clinical practice.