Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 7	**Synopsis No.:**
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Title of trial:	Investigation of the effect of food on the bioavailability of a 25 mg empagliflozin tablet and assessment of dose proportionality between 10 mg and 25 mg empagliflozin tablets in an open, randomised, single dose, three-period cross-over study in healthy male and female subjects
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Birkendorfer Strasse 65, Biberach, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	The objectives of the trial were to investigate the effect of food on the bioavailability of a 25 mg empagliflozin tablet as well as to assess dose proportionality between 10 mg and 25 mg empagliflozin tablets under fasting conditions.
Methodology:	This was an open-label, randomised, 3-way cross-over trial with 3 treatments (A, B, and C) and 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA). Each administration of trial medication was to be separated by a washout period of at least 7 days.
No. of subjects:	
planned:	Entered: 18 male and female subjects (at least 6 of each gender)
actual:	Entered: 18 subjects (9 male and 9 female subjects) Treatment A (25 mg empagliflozin, fasted): entered and treated: 18 subjects analysed (for primary endpoint): 18 subjects Treatment B (25 mg empagliflozin, fed): entered and treated: 18 subjects analysed (for primary endpoint): 17 subjects Treatment C (10 mg empagliflozin, fasted): entered and treated: 18 subjects analysed (for primary endpoint): 18 subjects

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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.
Test product 1:	Empagliflozin film-coated tablet
dose:	25 mg single dose
mode of admin.:	Oral
batch no.:	007768
Test product 2:	Empagliflozin film-coated tablet
dose:	10 mg single dose
mode of admin.:	Oral
batch no.:	007106
Duration of treatment:	Treatment A: Each subject received a single dose of 25 mg empagliflozin after an overnight fast of at least 10 h. Treatment B: Each subject received a single dose of 25 mg empagliflozin after a standardised high-fat, high-caloric breakfast. Treatment C: Each subject received a single dose of 10 mg empagliflozin after an overnight fast of at least 10 h. A washout period of at least 7 days was required between drug administrations in each of the 3 treatments.
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic parameters of empagliflozin were analysed as primary endpoints: $AUC_{0-\infty}$ and C_{max}. In addition, the following pharmacokinetic parameters of empagliflozin were assessed: AUC_{0-tz}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and V_z/F.
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, monitoring of adverse events, and tolerability assessment.

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Statistical methods:

To assess the effect of food on the pharmacokinetics of empagliflozin, point estimators (geometric means) of the intrasubject ratios of $AUC_{0-\infty}$ and C_{max} (under fed versus fasted conditions) and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used 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 residual error from ANOVA.

Intra-individual dose proportionality was explored under fasted conditions for the 25 mg and 10 mg single doses of empagliflozin using the overall power model on individual level. Point estimators for the slope parameter in this model and its 95% CI were computed for both $AUC_{0-\infty}$ and C_{max} of empagliflozin.

Descriptive statistics for primary and all other parameters were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

All 18 entered subjects completed the trial according to the clinical trial protocol. The trial population consisted of healthy male and female subjects. The mean age was 36.1 years, ranging from 21 to 51 years, and the mean BMI was 24.54 kg/m^2, ranging from 21.0 to 29.0 kg/m^2. All subjects were white.

In all 3 treatments, empagliflozin plasma concentrations reached peak concentrations rapidly and then declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase.

Analysis of food effect

The mean (%CV) pharmacokinetic parameters of empagliflozin for treatments A and B are summarised in Table 1. Absorption was slightly faster after administration of 25 mg empagliflozin under fasted conditions (treatment A) than under fed conditions (treatment B). Empagliflozin exposure ($AUC_{0-\infty}$ and C_{max}) under fasted conditions was higher than under fed conditions.

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Clinical pharmacology results (continued):

Table 1 Mean (%CV) pharmacokinetic parameters of empagliflozin in treatments A and B

Parameter	25 mg empagliflozin fasted (treatment A) N=18	25 mg empagliflozin fed (treatment B) N=17
$AUC_{0-\infty}$ [nmol·h/L]	5550 (26.0)	4650 (24.8)
C_{max} [nmol/L]	867 (26.8)	542 (27.7)
t_{max} [h]	1.38 (60.6)	2.22 (43.7)

The results of the relative bioavailability analysis of 25 mg empagliflozin with food (treatment B) versus 25 mg empagliflozin under fasted conditions (treatment A) are summarised in Table 2. The gMean ratios and 90% CIs were compared with the standard bioequivalence criteria of 80% to 125%. The overall exposure ($AUC_{0-\infty}$) was within the standard bioequivalence range. Comparable results were obtained for AUC_{0-tz}. However, the peak concentrations (C_{max}) were below the standard bioequivalence boundaries. For all 3 parameters, the 90% CIs excluded 100%.

Table 2 Relative bioavailabilities of 25 mg empagliflozin under fed versus fasted conditions (treatment B versus treatment A)

Parameter	gMean ratio (fed versus fasted conditions) [%][1]	95% CI for gMean ratio	
		Lower limit [%]	Upper limit [%]
$AUC_{0-\infty}$	84.04	80.86	87.34
C_{max}	63.22	56.74	70.44
AUC_{0-tz}	83.53	80.46	86.72

[1] For calculation of gMean in treatment A, the data of 18 subjects were used (N=18). For calculation of gMean in treatment B, the data of 17 subjects were used (N=17).

Assessment of dose proportionality

The mean (%CV) pharmacokinetic parameters of empagliflozin for treatments C and A are summarised in Table 3. Peak plasma concentrations were reached at a similar time after administration of 10 mg or 25 mg empagliflozin under fasted conditions (treatments C and A). As expected, empagliflozin exposure increased with the dose.

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Clinical pharmacology results (continued):

Table 3 Mean (%CV) pharmacokinetic parameters of empagliflozin in treatments C and A

Parameter	10 mg empagliflozin fasted (treatment C) N=18	25 mg empagliflozin fasted (treatment A) N=18
$AUC_{0-\infty}$ [nmol·h/L]	2360 (26.7)	5550 (26.0)
C_{max} [nmol/L]	377 (26.2)	867 (26.8)
t_{max} [h]	1.09 (27.3)	1.38 (60.6)

The gMean pair-wise ratios of $AUC_{0-\infty}$ and C_{max} after administration of 25 mg empagliflozin (treatment A) versus 10 mg empagliflozin (treatment C) were slightly lower than the dose ratio of 2.5 (gMean (95%CI): 2.36 (2.28 to 2.44) and 2.30 (2.08 to 2.53), respectively). The results of the log-transformed linear regression model show that the increase of $AUC_{0-\infty}$ and C_{max} between 10 mg and 25 mg empagliflozin was slightly less then dose proportional. The 95% CIs for the slope of C_{max} included 1. However, the corresponding interval of $AUC_{0-\infty}$ did not include 1 (see Table 4).

Table 4 Summary of the log-transformed linear regression model

Parameter	Slope β[1] N=18	95% CI for slope β	
		Lower limit	Upper limit
$AUC_{0-\infty}$	0.94	0.90	0.97
C_{max}	0.91	0.80	1.01

Safety results:

Each of the 18 subjects received 1 single 25 mg dose of empagliflozin both in treatments A and B and 1 single 10 mg dose of empagliflozin in treatment C as planned.

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Safety results (continued):

A total of 8 subjects (44.4%) reported at least 1 adverse event in at least 1 of the 3 treatment periods. The frequency of subjects with adverse events was highest during the treatment period '10 mg empagliflozin fasted' (treatment C, 4 subjects, 22.2%), followed by '25 mg empagliflozin fasted' and '25 mg empagliflozin fed' (treatments A and B, 2 subjects, 11.1%, each). The most frequently reported on-treatment adverse events at the system organ class (SOC) level were nervous system disorders, which were experience by a total of 5 subjects (27.8%). Gastrointestinal disorders were reported by 2 subjects (11.1%). The most frequent adverse event by preferred term was headache (3 subjects, 16.7%), followed by vomiting (2 subjects, 11.1%). All other adverse events were reported by 1 subject (5.6%) each. No clustering of any specific adverse event during any treatment was apparent.

The investigator classified adverse events of 2 subjects as related to the treatment: headache in subject [redacted] during the treatment period '10 mg empagliflozin fasted' (treatment C), and vertigo, abdominal pain, nausea and vomiting in subject [redacted] during the treatment period '25 mg empagliflozin fed' (treatment B). The adverse events abdominal pain, nausea, and vomiting of subject [redacted] were judged as related to the trial treatment, because this subject did not tolerate the high-fat breakfast served as part of the trial treatment in this treatment period. All other adverse events were judged as not drug-related. Three adverse events (nausea, vomiting, and presyncope), reported by subject [redacted] during the treatment period '25 mg empagliflozin fed' (treatment B), were classified as severe. Two of these 3 severe adverse events (nausea and vomiting) were also assessed as related to the trial treatment (as described above). All other adverse events were of mild or moderate intensity. No serious adverse events and no adverse events leading to trial discontinuation were reported in this trial.

In this trial, there were no clinically relevant findings or abnormalities with respect to the clinical laboratory measurements, ECG recordings, vital sign measurements, and the physical examination. The investigator rated the tolerability of treatment A (25 mg empagliflozin fasted) as 'good' for all 18 subjects. Regarding treatment B (25 mg empagliflozin fed), the tolerability was rated as 'good' for 17 subjects and as 'not satisfactory' for 1 subject (subject [redacted], see above). With respect to treatment C (10 mg empagliflozin fasted), the tolerability was rated as 'good' for 17 subjects and as 'satisfactory' for 1 subject (subject [redacted] see above).

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Conclusions:

Administration of empagliflozin with food resulted in a small decrease in empagliflozin exposure, with $AUC_{0-\infty}$ being 16% lower and C_{max} being 37% lower under fed than under fasted conditions. The clinical relevance of this slight effect of food on empagliflozin pharmacokinetics has to be evaluated based on additional data from other long-term clinical trials.

As the gMean values of $AUC_{0-\infty}$ and C_{max} increased slightly less than dose proportionally between 10 mg and 25 mg empagliflozin, the slope β of the regression line was slightly less than 1 (0.94 and 0.91, respectively). The 95% CIs for the slope of C_{max} included 1 and the corresponding intervals of $AUC_{0-\infty}$ did not include 1. However, the point estimate and the corresponding 95% CIs were close to 1 for both parameters and therefore it can be concluded that empagliflozin exposure increased roughly dose proportionally between 10 mg and 25 mg empagliflozin.

Administration of a single dose of either 10 mg or 25 mg empagliflozin under fasted conditions as well as 25 mg empagliflozin under fed conditions was generally well tolerated by the healthy male and female subjects in this trial.