Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-016154-40	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 8	**Synopsis No.:**
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Title of trial:	A randomised, double-blind, placebo-controlled parallel group efficacy and safety trial of BI 10773 (10 and 25 mg administered orally once daily) over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite a background therapy of pioglitazone alone or in combination with metformin
Coordinating Investigators:	[redacted]
Trial sites:	Multi-centre trial: 69 trial sites in 8 countries (Canada, China, Greece, India, Philippines, Thailand, Ukraine, USA)
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin (10 and 25 mg once daily) compared with placebo given for 24 weeks as add-on therapy to pioglitazone alone or pioglitazone in combination with metformin in patients with type 2 diabetes mellitus with insufficient glycaemic control.
Methodology:	Randomised, double-blind, placebo-controlled, parallel group comparison. A 2-week open-label placebo run-in period preceded randomisation. Randomisation was stratified by HbA_{1c} at screening, renal function at screening, and background medication. Patients who completed the planned 24-week treatment period in this trial were eligible to continue their randomised treatment by enrolling in an extension trial (BI trial 1245.31). Patients who did not enter the extension trial were to be followed up for 1 week.
No. of subjects:	
planned:	Entered: 468

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actual:	Enrolled: 762 Placebo: Entered: 166 treated: 165 analysed (for primary endpoint): 165 Empagliflozin 10 mg: Entered: 165 treated: 165 analysed (for primary endpoint): 165 Empagliflozin 25 mg: Entered: 168 treated: 168 analysed (for primary endpoint): 168
Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus and insufficient glycaemic control (HbA_{1c} ≥7.0% and ≤10.0%) despite therapy of pioglitazone alone or in combination with metformin; age ≥18 years (≤65 years in India only); BMI ≤45 kg/m^2
Test product:	Empagliflozin tablets 10 mg; empagliflozin tablets 25 mg
dose:	10 or 25 mg once daily
mode of admin.:	Oral
batch no.:	Empagliflozin 10 mg: 909474A, 003436 Empagliflozin 25 mg: 909473A, 909472A, 003531
Reference therapy:	Placebo tablets matching empagliflozin 10 mg or 25 mg tablets
dose:	Not applicable
mode of admin.:	Oral
batch no.:	Matching empagliflozin 10 mg: 84835, 84870, 85254, 88494 Matching empagliflozin 25 mg: 85114, 85092, 88655
Duration of treatment:	Two-week placebo run-in; 24-week treatment period; 1-week follow-up period. Background medication was to be taken during the entire trial (including placebo run-in period) with dosage unchanged.
Criteria for evaluation:	
Efficacy:	The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The key secondary endpoints were the changes from baseline in fasting plasma glucose (FPG) and in body weight after 24 weeks of treatment.

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Safety:	Adverse events (AEs), Clinical Event Committee-adjudicated events, and adverse events of special interest (AESIs) including protocol-specified significant AEs (decreased renal function and hepatic injury), hypoglycaemic events, urinary tract infections, genital infections, and volume depletion; change from baseline in clinical laboratory assessments, vital signs, and 12-lead ECG.
Statistical methods:	Each dose of empagliflozin (10 or 25 mg) was independently compared to placebo. The hypotheses were tested in a pre-specified hierarchical sequence (primary endpoint, first key secondary endpoint, second key secondary endpoint, and primary endpoint for patients with pioglitazone in combination with metformin background therapy). The analysis of the primary endpoint for patients with pioglitazone alone background therapy was removed from the hierarchical sequence and only performed as an exploratory analysis due to the reduced patient number after the implementation of a protocol amendment. The overall significance level for the trial is $\alpha = 5\%$ (2-sided); α was spent equally between the 2 test sequences for the 2 doses (i.e. 2.5% on each test). Each step in either test sequence was only regarded as 'confirmatory' if the null hypothesis tested before was rejected. If at any step the null hypothesis was not rejected, the subsequent step(s) of that dose level were regarded as 'exploratory'. Primary analysis: analysis of covariance (ANCOVA); the model included treatment, background medication, and renal function as fixed effects, and baseline HbA_{1c} as a linear covariate (and the respective efficacy variable at baseline as another linear covariate for secondary endpoints). Sensitivity analyses were carried out using ANCOVA based on different analysis sets and imputation methods; in addition, a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach was used to analyse changes over time for efficacy variables. Continuous exploratory endpoints were analysed using a similar model as for the primary analysis. Categorical exploratory endpoints were tabulated. Binary exploratory endpoints were analysed using logistic regression. Safety: descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 762 patients enrolled in this study, 499 were randomised; 166 patients were randomised to the placebo group, 165 to the empagliflozin 10 mg group, and 168 to the empagliflozin 25 mg group. All but 1 patient in the placebo group were treated with at least 1 dose of study medication. Of the 499 randomised patients, 54.3% were from Asia (China, India, the Philippines, and Thailand), 17.2% from Europe (Greece and Ukraine), and 28.5% from North America (Canada and USA). Of the treated patients, 10.9% in the placebo group, 6.7% in the empagliflozin 10 mg group, and 7.1% in the empagliflozin 25 mg group discontinued study medication prematurely, with the most common reason being adverse events. Overall, 91.8% of the treated patients completed the trial; 61.2% of the treated patients continued in the extension study (trial 1245.31).

The demographics and baseline characteristics were in general balanced among the 3 treatment groups. The proportion of male patients was 48.4%. Most patients were Asian (57.8%) or White (39.6%). More than half of the patients (56.0%) were diagnosed with type 2 diabetes for up to 5 years. Mean (standard deviation) age was 54.5 (9.8) years, BMI 29.2 (5.5) kg/m^2, baseline HbA_{1c} 8.09% (0.88%), baseline FPG 151.9 (38.5) mg/dL, and baseline body weight 78.3 (19.7) kg. About 3 quarters of the patients (75.5%) had a background therapy of metformin plus pioglitazone; the rest had a background therapy of pioglitazone alone.

Efficacy analyses were mainly based on the full analysis set (FAS), which included all treated patients.

Compared with placebo treatment, both empagliflozin 10 and 25 mg treatments showed statistically significant reductions from baseline in HbA_{1c} (primary endpoint), in FPG, and in body weight (key secondary endpoints). Additionally, placebo-adjusted reduction from baseline in HbA_{1c} was statistically significant in patients receiving empagliflozin treatments added on to a background therapy of pioglitazone in combination with metformin. The results from the ANCOVA models are summarised in the table below.

All sensitivity analyses (based on different analysis sets, imputation methods, or models) for all primary and key secondary endpoints showed results consistent with the main analysis for the respective endpoint, with regard to placebo-corrected adjusted mean and 95% confidence interval.

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Efficacy results continued:

Primary and key secondary endpoints

Change from baseline at Week 24	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA_{1c} [%]			
Baseline mean (standard error (SE))	8.16 (0.07)	8.07 (0.07)	8.06 (0.06)
Adjusted mean change (SE)	-0.11 (0.07)	-0.59 (0.07)	-0.72 (0.07)
Placebo-corrected adjusted mean (SE)		-0.48 (0.09)	-0.61 (0.09)
97.5% confidence interval		-0.69, -0.27	-0.82, -0.40
p-value		<0.0001	<0.0001
FPG [mg/dL]			
Baseline mean (SE)	151.93 (3.14)	152.01 (2.99)	151.86 (2.86)
Adjusted mean change (SE)	6.47 (2.61)	-17.00 (2.63)	-21.99 (2.59)
Placebo-corrected adjusted mean (SE)		-23.48 (3.71)	-28.46 (3.68)
97.5% confidence interval		-31.81, -15.15	-36.73, -20.19
p-value		<0.0001	<0.0001
Body weight [kg]			
Baseline mean (SE)	78.10 (1.57)	77.97 (1.49)	78.93 (1.54)
Adjusted mean change (SE)	0.34 (0.21)	-1.62 (0.21)	-1.47 (0.21)
Placebo-corrected adjusted mean (SE)		-1.95 (0.30)	-1.81 (0.30)
97.5% confidence interval		-2.64, -1.27	-2.49, -1.13
p-value		<0.0001	<0.0001
HbA_{1c} [%], for patients with pioglitazone in combination with metformin background therapy			
Baseline mean (SE)	8.15 (0.08)	8.07 (0.08)	8.10 (0.07)
Adjusted mean change (SE)	-0.11 (0.08)	-0.55 (0.08)	-0.70 (0.07)
Placebo-corrected adjusted mean (SE)		-0.45 (0.11)	-0.60 (0.11)
97.5% confidence interval		-0.69, -0.21	-0.83, -0.36
p-value		<0.0001	<0.0001

Adjusted values: based on ANCOVA last observation carried forward using full analysis set, data after the initiation of rescue therapy were excluded

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Efficacy results continued:	Other exploratory efficacy endpoints assessed were: the change in HbA_{1c} and in FPG over time, the change from baseline at Week 24 in blood pressure and in waist circumference, the proportion of patients with treat-to-target HbA_{1c} response at Week 24 (HbA_{1c} below 7.0%, HbA_{1c} below 6.5%, or HbA_{1c} lowered by at least 0.5% from baseline), the proportion of patients with treat-to-target body weight response at Week 24 (reduction by more than 5% from baseline), the proportion of patients with treat-to-target blood pressure response at Week 24 (SBP <130 mmHg and DBP <80 mmHg), the proportion of patients who achieved all the targets in the composite endpoint (reduction at Week 24 from baseline in HbA_{1c} by >0.5%, in SBP by >3 mmHg, and in body weight by >2%), and the use of rescue therapy. The results of all of these analyses showed better treatment effects in the empagliflozin 10 and 25 mg groups than in the placebo group.
Safety results:	Exposure to study medication was balanced among groups, with mean exposures (SD) of 164.6 (30.2) days in the placebo group, 165.2 (30.5) days in the empagliflozin 10 mg group, and of 165.0 (28.6) days in the empagliflozin 25 mg group. Overall, the frequency of patients with adverse events was similar in the placebo group (72.7%), empagliflozin 10 mg group (67.3%), and empagliflozin 25 mg (71.4%) group. The highest frequency of adverse events was reported for the MedDRA system organ class 'infections and infestations', with frequencies of 29.1% in the placebo group, 29.1% in the empagliflozin 10 mg group, and 31.0% in the empagliflozin 25 mg group. Serious adverse events were reported for 7 patients (4.2%) in the placebo group, 7 patients (4.2%) in the empagliflozin 10 mg group, and 6 patients (3.6%) in the empagliflozin 25 mg group. No SAE, at the PT level, was reported for more than 1 patient in each treatment group. Three deaths were reported during this study, 1 in the placebo group and 2 in the empagliflozin 25 mg group. Premature discontinuation of study medication due to adverse events was reported for 4 patients (2.4%) in the placebo group, for 2 patients (1.2%) in the empagliflozin 10 mg group, and 5 patients (3.0%) in the empagliflozin 25 mg group. No AE leading to premature discontinuation, at the PT level, was reported for more than 1 patient in each treatment group.

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Safety results continued:

The overall frequencies of adverse events assessed as drug-related by the investigator were similar among all 3 treatments, with 18.8% in the placebo group, 14.5% in the empagliflozin 10 mg group, and 18.5% in the empagliflozin 25 mg group.

Confirmed hypoglycaemic events were reported for 3 patients (1.8%) in the placebo group, for 2 patients (1.2%) in the empagliflozin 10 mg group, and for 4 patients (2.4%) in the empagliflozin 25 mg group. All episodes were of mild intensity.

Mean changes (SD) from baseline to Week 24 in serum creatinine were 0.3 (9.5) µmol/L in the placebo group, 1.4 (9.9) µmol/L in the empagliflozin 10 mg group, and 1.9 (10.9) µmol/L in the empagliflozin 25 mg group. Mean changes (SD) from baseline to Week 24 in eGFR (based on MDRD formula) were -0.5 (12.5) mL/min/1.73m^2 in the placebo group, -2.1 (14.4) mL/min/1.73m^2 in the empagliflozin 10 mg group, and -3.4 (15.6) mL/min/1.73m^2 in the empagliflozin 25 mg group.

The frequency of urinary tract infections, based on a MedDRA search of reported adverse events, was similar to placebo (16.4%) in the empagliflozin 10 mg group (17.0%) and lower than placebo in the empagliflozin 25 mg group (11.9%). The frequency of genital infections, based on a MedDRA search of reported adverse events, was 2.4% in the placebo group, 8.5% in the empagliflozin 10 mg group, and 3.6% in the 25 mg group.

Bone fractures, based on a MedDRA search of reported adverse events, were reported for 4 patients (2.4%) in the placebo group, for 2 patients (1.2%) in the empagliflozin 10 mg group, and for 1 patient (0.6%) in the empagliflozin 25 mg group.

Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, and plasma proteins were negligible. Mean haematocrit values decreased from baseline to last value on treatment in the placebo group but increased in the 2 empagliflozin groups. Mean uric acid values increased from baseline to last value on treatment in the placebo group but decreased in the 2 empagliflozin groups.

A numerical increase was seen in empagliflozin 10 mg group in the placebo-corrected adjusted mean change from baseline to Week 24 for HDL cholesterol. No relevant changes in total cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio, or triglycerides were observed.

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Conclusions:

In this randomised, double-blind study, treatments with empagliflozin 10 and 25 mg/day for 24 weeks were compared with placebo treatment, added on to a background therapy of pioglitazone alone or in combination with metformin, in patients with type 2 diabetes and insufficient glycaemic control. Compared with placebo, both empagliflozin 10 and 25 mg treatments showed statistically significant and clinically meaningful reductions from baseline in HbA_{1c}, in fasting plasma glucose, and in body weight after 24 weeks. The safety profile was similar to placebo for both empagliflozin groups. Hypoglycaemic events overall were rare and occurred at similar frequencies in the placebo group and the 2 empagliflozin groups. Adverse events related to urinary tract infection did not increase in frequency with empagliflozin treatment. Genital infections were observed more frequently with empagliflozin treatment but were manageable with standard therapy and did not lead to treatment discontinuation.