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.:** 2010-019968-37	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 SEP 2013	**Trial No. / U No.:** 1245.49 / U13-2122-01	**Dates of trial:** 02 MAR 2011 – 22 APR 2013	**Date of revision:** Not applicable

Title of trial:	A phase III, randomized, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre trial, with 104 trial sites in 14 countries: Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Russia, Spain, Ukraine, Colombia, Guatemala, Mexico, Peru, USA
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the safety and efficacy of empagliflozin (10 mg and 25 mg once daily) compared with placebo, added to an insulin regimen of multiple daily injections (MDI) alone or with metformin in patients with type 2 diabetes and insufficient glycaemic control
Methodology:	Randomised, double-blind, placebo-controlled, treat-to-target, parallel group comparison. Patients were recruited and randomised within their background medication at a 1:1:1 ratio to placebo, empagliflozin 10 mg, or empagliflozin 25 mg. Randomisation was stratified by HbA_{1c}, eGFR, background medication at Visit 1, and geographic region. A 2-week open-label placebo run-in period preceded randomisation. The total randomised treatment period was of 52 weeks. Patients were to be followed-up for 4 weeks after completing the trial or until the end of study after prematurely discontinuing trial medication.
No. of patients:	
planned:	entered: 555 patients (185 patients per treatment group)
actual:	enrolled: 1171 patients Placebo: entered: 189 treated: 188 analysed (for primary endpoint): 188 Empagliflozin 10 mg: entered: 187 treated: 186 analysed (for primary endpoint): 186 Empagliflozin 25 mg: entered: 190 treated: 189 analysed (for primary endpoint): 189

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Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus on a background therapy with an MDI insulin regimen (total insulin >60 IU/day), either alone or in combination with metformin; HbA_{1c} 7.5% to 10%, age ≥18 years, BMI 30 to 45 kg/m^2 at screening.
Test product:	Empagliflozin film-coated tablet
dose:	10 or 25 mg once daily
mode of admin.:	Oral
batch no.:	001746 and 004897 (10 mg); 001747A and 003530C (25 mg)
Reference therapy:	Placebo matching empagliflozin 10 mg tablets and placebo matching empagliflozin 25 mg tablets
dose:	Not applicable
mode of admin.:	Oral
batch no.:	88494 and 88608 (matching 10 mg); 88655 and 88683 (matching 25 mg)
Duration of treatment:	The total treatment duration was of 52 weeks, after the 2-week placebo run-in period. From Week 1 to Week 18, patients were to maintain a stable insulin dose and were treated with either empagliflozin 10 mg, empagliflozin 25 mg, or placebo. From Week 19 to 40, treat-to-target insulin dose adjustements were to be made as needed in order to achieve glucose treat-to-target values. From Week 41 to Week 52, patients were to maintain a stable insulin dose, and adjustements were to be made for safety reasons only. In addition, patients were to be followed-up for 4 weeks after completing the trial or until the end of study after prematurely discontinuing study medication.

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Criteria for evaluation:

Efficacy:

The primary endpoint was the change from baseline in HbA_{1c} after 18 weeks of treatment.

The key secondary endpoints were the change from baseline in total insulin daily dose after 52 weeks of treatment, the change from baseline in body weight after 52 weeks of treatment, and the change from baseline in HbA_{1c} after 52 weeks of treatment.

Additional exploratory efficacy endpoints were defined; of note being the proportion of patients with HbA_{1c} <7% after 18 and 52 weeks of treatment.

Safety:

Adverse events (AEs), Clinical Event Committee-adjudicated cardiovascular events, and AEs of special interest, including protocol-specified significant AEs (decreased renal function and hepatic injury), hypoglycaemic events, urinary tract infection, genital infection, and volume depletion; change from baseline in clinical laboratory values, vital signs, and 12-lead electrocardiograms.

Statistical methods:

For the primary endpoint, the testing of the superiority hypothesis versus placebo was realised with an analysis of covariance (ANCOVA) with treatment, background therapy, geographical region, and baseline renal function as fixed classification effects and baseline HbA_{1c} as linear covariate. The ANCOVA was conducted on the full analysis set at Week 18 (FAS-18) of patients. Missing data was imputed using the last observation carried forward (LOCF) approach. An ANCOVA similar to the one used for the primary endpoint was applied for the key secondary endpoints on the per-protocol completers set at Week 52 (PPS-completers-52) of patients. The confirmatory analyses for the primary endpoint and for the key secondary endpoints was based on two-sided tests at a 2.5% level (and corresponding 97.5% confidence intervals (CIs)) for the treatment difference between each of the 2 empagliflozin doses and placebo, apart from the non-inferiority comparisons, which was one-sided at a 1.25% level. All other exporatory tests were two-sided tests at a 5% level (and corresponding 95% confidence intervals).

The primary endpoint and the key secondary endpoints were tested in the following hierarchical order: change from baseline in HbA_{1c} at Week 18, change from baseline in total insulin dose at Week 52, change from baseline in body

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weight at Week 52, change from baseline in HbA_{1c} at Week 52 (non-inferiority), change from baseline in HbA_{1c} at Week 52 (superiority).

The proportion of patients with HbA_{1c} <7% after 18 and 52 weeks of treatment (binary endpoints) were analysed using logistic regression. Odds ratios and their respective 95% CIs and p-values were obtained. Exact 95% CIsfor proportions were obtained, where appropriate. For safety and all other efficacy endpoints, descriptive statistics was used.

SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 1171 patients enrolled, 566 patients were entered and 563 were treated. Overall, 84.4% of the patients treated with randomised study medication (83.5% placebo, 83.3% empagliflozin 10 mg, and 86.2% empagliflozin 25 mg) completed the 52-week treatment period. A total of 15.6% of patients prematurely discontinued trial medication, the most frequent reason being adverse events (28 patients, 5.0%). Overall, 95.6% of all patients had an acceptable compliance of 80 to 120%, based on tablet count of dispensed and returned medication at each visit. In total, 45.5% of the participants were male and 94.3% were White. The mean age (SD) at baseline was 56.7 (9.5) years and the mean body mass index (SD) at baseline was 34.79 (4.06) kg/m^2.

Baseline efficacy variables, analysed on the full analysis set (FAS), were balanced across groups; the mean HbA_{1c} (SD) at baseline was 8.34 (0.73)%, the mean total daily insulin dose (SD) was 92.0 (44.3) IU, the mean body weight (SD) was 96.2 (17.5) kg, the mean SBP (SD) was 133.3 (15.5) mmHg, and the mean DBP (SD) was 78.8 (8.6) mmHg; 71.0% of patients had a combined insulin and metformin antidiabetic background medication (65.7% of all patients in the FAS had ≥1500 mg metformin per day) and 29.0% of patients had an insulin only antidiabetic background medication. The mean daily metformin dose (SD) was 2026.8 (542.2) mg. Overall, 78.0% of patients had a history of hypertension, with controlled BP in 29.7% of patients. Two thirds of all patients had type 2 diabetes for >10 years.

The results of the main analyses of the primary and key secondary endpoints, including CIs and p-values, are shown in the table below. All steps in the hierarchical testing sequence were succesful and treatment with both empagliflozin doses showed statistical superiority compared with placebo.

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Change in primary [1] and key secondary endpoints [2] from baseline (ANCOVA)

	Placebo	Empagliflozin	
		10 mg	25 mg
Primary endpoint: HbA_{1c} [%] [1]			
Baseline mean (SE)	8 33 (0 05)	8 39 (0 05)	8 29 (0 05)
Placebo-adjusted mean change from baseline (SE) at Week 18		-0 44 (0 08)	-0 52 (0 07)
97 5% CI		(-0 61,-0 27)	(-0 69,-0 35)
p-value		<0 0001	<0 0001
Key secondary endpoints [2]			
Total daily insulin dose [IU/day]			
Baseline mean (SE)	89 94 (4 08)	88 57 (3 43)	90 38 (4 09)
Placebo-adjusted mean change from baseline (SE) at Week 52		-8 83 (3 05)	-11 22 (3 05)
97 5% CI		(-15 69,-1 97)	(-18 09,-4 36)
p-value		0 0040	0 0003
Body weight [kg]			
Baseline mean (SE)	96 34 (1 63)	96 47 (1 53)	95 37 (1 73)
Placebo-adjusted mean change from baseline (SE) at Week 52		-2 39 (0 51)	-2 48 (0 51)
97 5% CI		(-3 54,-1 24)	(-3 63,-1 33)
p-value		<0 0001	<0 0001
HbA_{1c} [%]			
Baseline mean (SE)	8 25 (0 07)	8 40 (0 07)	8 37 (0 06)
Placebo-adjusted mean change from baseline (SE) at Week 52		-0 38 (0 11)	-0 46 (0 11)
97 5% CI		(-0 62,-0 13)	(-0 70,-0 22)
p-value non-inferiority [3]		<0 0001	<0 0001
p-value superiority		0 0005	<0 0001

[1] primary endpoint, Full Analysis Set-18 (LOCF-18); stable insulin background
[2] key secondary endpoints, Per Protocol Set completers-52 (LOCF-52), change at Week 52, following a treat-to-target period from Week 19 to Week 40
[3] one-sided test relative to 0 3

Overall, better treatment effects in other exploratory endpoints were seen with empagliflozin treatment compared with placebo treatment. Of note are the higher proportion of patients reaching HbA_{1c}<7% with empagliflozin treatment than with placebo treatment, both at Week 18 (16.0% placebo, 19.9% empagliflozin 10 mg, 31.2% empagliflozin 25 mg) and at Week 52 (21.8% placebo, 31.7% empagliflozin 10 mg, and 41.3% empagliflozin 25 mg).

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Safety results:

The mean exposure (SD) was: 337.6 (78.0) days in the placebo group, 335.3 (78.4) days in the empagliflozin 10 mg group, and 339.4 (81.9) days in the empagliflozin 25 mg group. The percentage of patients with treatment-emergent AEs was: 89.9% in the placebo group, 86.0% in the empagliflozin 10 mg group, and 84.7% in the empagliflozin 25 mg group. The highest frequency of AEs was reported for the MedDRA system-organ class 'metabolism and nutrition disorders': 65.4% for placebo, 59.1% for empagliflozin 10 mg, and 61.4% for empagliflozin 25 mg. Adverse events of severe intensity were reported for 12 patients (6.4%) in the placebo group, 19 patients (10.2%) in the empagliflozin 10 mg group, and 26 patients (13.8%) in the empagliflozin 25 mg group. Drug-related AEs (as assessed by the investigator) were reported for 34.0% patients in the placebo group, 30.1% patients in the empagliflozin 10 mg group, and 40.2% patients in the empagliflozin 25 mg group. The frequencies of patients with AEs leading to premature discontinuation of trial medication were: 4.8% (9 patients) in the placebo group, 5.4% (10 patients) in the empagliflozin 10 mg group, and 4.8% (9 patients) in the empagliflozin 25 mg group. Serious AEs were reported for 22 patients (11.7%) in placebo group, 20 patients (10.8%) in the empagliflozin 10 mg group, and 22 patients (11.6%) in the empagliflozin 25 mg group. One patient in the empagliflozin 25 mg died in this study; the cause of death was metastatic lung cancer.

Confirmed hypoglycaemic events were reported for 58.0% of the patients in the placebo group, 51.1% in the empaglilflozin 10 mg, and 57.7% in the empagliflozin 25 mg group. The number of severe episodes among these (requiring assistance) was: 3 patients (1.6%) each in the placebo group and empagliflozin 10 mg group and 1 patient (0.5%) in the empagliflozin 25 mg group; episodes of severe intensity were reported for 2 patients (1.1%) in the placebo group and 3 patients (1.6%) in each empagliflozin group. One event (0.5%, empagliflozin 10 mg) required/prolongued hospitalisation of the patient. On a fixed dose of insulin background therapy, confirmed hypoglycaemic events at Week 18 were reported for 37.2% of the patients in the placebo group, 39.8% in the empagliflozin 10 mg group, and 41.3% in the empagliflozin 25 mg group.

The mean changes from baseline in creatinine, cystatine C, and in estimated glomerular filtration rate (eGFR MDRD) in the randomised groups were small and comparable across treatment groups at Week 52; these parameters were returning to baseline values at follow-up.

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Conclusions:	Two patients in the empagliflozin 10 mg group and 2 patients in the empagliflozin 25 mg group were reported with events related to acute renal failure. No potential Hy's law case was reported in this study. Urinary tract infections were reported for 29 patients (15.4%) in the placebo group, 29 patients (15.6%) in the empagliflozin 10 mg group, and 29 patients (15.3%) in the empagliflozin 25 mg group. Genital infections were reported for 3 patients (1.6%) in the placebo group, 8 patients (4.3%) in the empagliflozin 10 mg group, and 18 patients (9.5%) in the empagliflozin 25 mg group. Overall, there were no clinically meaningful changes from baseline in safety laboratory parameters (differential blood cell counts; blood or urine levels of electrolytes, enzymes, substrates and proteins) after 52 weeks of treatment. Small increases in haematocrit were higher with empagliflozin than with placebo. Haemoglobin slightly increased with empagliflozin treatment and remained constant with placebo. Numerical decreases compared with placebo were seen in LDL/HDL cholesterol ratio for empagliflozin 10 mg, non-HDL cholesterol for empagliflozin 10 mg, and triglycerides for empagliflozin 25 mg; numerical increases in HDL-cholesterol were seen for both empagliflozin doses. These parameters were returning to baseline values at follow-up. Pulse rate changes were overall small and did not increase with empagliflozin treatment. In this 52-week study, empagliflozin 10 mg and 25 mg once daily led to a significant reduction in HbA_{1c} after 18 weeks of treatment compared with placebo, on a stable MDI insulin dose regimen, with or without metformin background therapy. After a dedicated treat-to-target period, empagliflozin 10 mg and 25 mg once daily resulted in significantly greater reductions in HbA_{1c} and greater proportions of patients reaching an HbA_{1c} value of <7% at Week 52 compared with placebo, despite significantly less insulin use and without an increase in confirmed hypoglycaemic AEs. In addition, treatment with both empagliflozin doses once daily led to significant reductions in body weight at Week 52 compared with placebo treatment. Both empagliflozin doses were well tolerated, with overall AE rates comparable with placebo. The percentage of patients with urinary tract infections was similar between placebo and both doses of empagliflozin. More patients reported genital infections with empagliflozin treatment than with placebo treatment.