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.:** 2009-016243-20	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date: 30 APR 2014	**Trial No. / U No.:** 1245.20 / U12-1517-01	**Dates of trial:** 12 AUG 2010–19 MAR 2012	**Date of revision:** Not applicable

Title of trial:	A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 and sitagliptin administered orally over 24 weeks, in drug naïve patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise
Coordinating Investigators:	[redacted] Germany [redacted] China
Trial sites:	Multi-centre trial: 124 trial sites in 9 countries (Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, 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 mg or 25 mg once daily) compared with placebo and sitagliptin given for 24 weeks as monotherapy in drug-naïve patients with type 2 diabetes mellitus and insufficient glycaemic control. Open-label (OL) arm: to assess the efficacy and safety of empagliflozin 25 mg once daily in patients with type 2 diabetes and very poor glycaemic control (HbA_{1c} >10%).
Methodology:	Randomised, double-blind, active and placebo-controlled, parallel-group comparison. Randomisation was stratified by HbA_{1c} at screening, renal function at screening, and geographical region. A 2-week open-label placebo run-in period preceded randomisation. Patients allocated to the open-label arm started treatment with empagliflozin 25 mg without a run-in period. Patients who completed the planned 24-week randomised treatment period in this trial were eligible to continue their randomised treatment by enrolling in the extension trial BI 1245.31. Patients who did not enter the extension trial were to be followed-up for 1 week.

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No. of subjects:	
planned:	entered: 920, including 80 in the open-label arm
actual:	enrolled: 1616 entered: 986 Empagliflozin 10 mg: entered: 224 treated: 224 analysed (for primary endpoint): 224 Empagliflozin 25 mg: entered: 224 treated: 224 analysed (for primary endpoint): 224 Sitagliptin 100 mg : entered: 223 treated: 223 analysed (for primary endpoint): 223 Placebo: entered: 228 treated: 228 analysed (for primary endpoint): 228 Open-label empagliflozin 25 mg: entered: 87 treated: 87 analysed (for primary endpoint): 87
Diagnosis and main criteria for inclusion:	Drug-naïve patients with type 2 diabetes mellitus and insufficient glycaemic control (HbA_{1c} ≥7.0% and ≤10.0%; Germany: ≥7.0 to ≤9.0%); age ≥18 years (Japan: ≥20 years; India: ≥18 years and ≤65 years); body mass index ≤45 kg/m^2. Patients with an HbA_{1c} of >10% and fulfilling all remaining inclusion criteria were eligible for inclusion in the empagliflozin 25 mg OL arm.
Test product:	Empagliflozin film-coated tablet
dose:	10 or 25 mg once daily
mode of admin.:	Oral
batch no.:	909476A and 003437A (10 mg); 909472A and 003533 (25 mg)

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Reference therapy:	Placebo matching empagliflozin 10 mg tablets, placebo matching empagliflozin 25 mg tablets, and placebo matching sitagliptin 100 mg tablets
dose:	Not applicable
mode of admin.:	Oral, tablets
batch no.:	84835 and 88367 (matching empagliflozin 10 mg); 85092 and 88627 (matching empagliflozin 25 mg); B091004832 and B101003628 (matching sitagliptin)
Reference therapy 2:	Sitagliptin tablets 100 mg
dose:	100 mg once daily
mode of admin.:	Oral, tablets
batch no.:	E07428-012F02
Duration of treatment:	Two-week placebo run-in (except for patients allocated to the OL arm); 24-week treatment period; 1-week follow-up period.
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 change from baseline in body weight and blood pressure (systolic, SBP and diastolic, DBP) after 24 weeks of treatment. Other endpoints were: occurrence of a treat-to-target response (HbA_{1c} after 24 weeks of treatment < 7.0%), occurrence of relative efficacy response (HbA_{1c} lowering by ≥0.5% after 24 weeks of treatment), changes in HbA_{1c} and fasting plasma glucose (FPG) by visit over time, FPG change from baseline after 24 weeks of treatment, use of rescue medication, the composite endpoint of the following conditions at Week 24 (all 3 had to be fulfilled): reduction from baseline in HbA_{1c} of ≥0.5%, reduction from baseline in SBP of >3 mmHg, and reduction from baseline in body weight of >2%.
Safety:	Adverse events, Clinical Event Committee-adjudicated cardiovascular events, and adverse events of special interest, including protocol-specified adverse events (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.

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Statistical methods:

Primary endpoint: Testing of superiority hypothesis versus placebo with an analysis of covariance (ANCOVA) with randomised treatment, geographical region, and renal function as fixed effects and baseline HbA_{1c} as covariate.

Key secondary endpoints: ANCOVA similar to primary endpoint

The overall type I error across the primary endpoint and key secondary endpoints was maintained at 2.5% using a hierarchical procedure for the comparisons of the 2 empagliflozin doses versus placebo. All other tests were two-sided at a 5% level (95% confidence interval). For all efficacy analyses, except for some sensitivity analyses of primary and secondary endpoints, data were censored at the date of first intake of a rescue medication.

The sitagliptin group comparison vs. placebo was used for internal validation of the trial. The comparison of sitagliptin to the 2 empagliflozin doses was used to evaluate (no confirmatory test) the degree of similarity of efficacy and safety between the 2 compounds (ICH E9 / ICH E10).

Safety and other efficacy endpoints: descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 1616 patients enrolled, 986 patients were entered and and all were treated. Overall, 89.3% of patients assigned to randomised treatment (82.0% of patients in the placebo treatment group, 92.0% of patients in the empagliflozin 10 mg group, 91.1% of patients in the empagliflozin 25 mg group, and 92.4% of patients in the sitagliptin group) and 89.7% of patients assigned to the OL arm completed the 24-week treatment period. A total of 10.7% of patients prematurely discontinued trial medication, the most frequent reason being patients' refusal to continue trial medication (30 patients, 3.3% in the randomised groups and 3 patients, 3.4% in the OL arm). Overall, 95.9% of all randomised patients and 93.1% of the patients from the OL arm showed an acceptable compliance of 80 to 120%, based on tablet count of dispensed and returned medication at each visit. In the randomised groups, 61.3% of the participants were male; 64.1% were Asian and 33.6% were White. The mean age at baseline was 55.0 years (SD 11.0 years) and the mean body mass index at baseline was 28.36 kg/m^2 (SD 5.59 kg/m^2). In the OL arm, 73.6% of the participants were male; 60.9% were Asian and 33.3% were White. The mean age at baseline was 50.2 years (SD 11.3 years) and the mean body mass index at baseline was 28.15 kg/m^2 (SD 5.50 kg/m^2).

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Efficacy results (cont.): Baseline efficacy variables were well balanced across the randomised groups; the mean HbA_{1c} at baseline was 7.88% (SD 0.82%), the mean body weight was 78.42 kg (SD 19.22 kg), the mean SBP was 131.4 mmHg (SD 16.6 mmHg), and the mean DBP was 79.1 mmHg (SD 9.6 mmHg); 50.7% of patients had a history of hypertension, with controlled BP (SBP <130 mm Hg and DBP <80 mmHg) in 38.0% of patients. Most patients had type 2 diabetes for <5 years. In the OL arm, the mean HbA_{1c} was 11.50% (SD 1.39%), the mean body weight was 80.72 kg (SD 19.52 kg), the mean SBP was 129.5 mmHg (SD 14.1 kg), and the mean DBP was 81.0 mmHg (SD 9.6 mmHg); 36.8% of patients had a history of hypertension, with controlled BP in 35.6% patients. Most patients had type 2 diabetes for ≤1 year.

The results of the main analyses of the primary and key secondary endpoints are shown in Table 1 below. Both empagliflozin doses demonstrated superiority over placebo for changes in HbA1c, body weight, and SBP after 24 weeks of treatment. Statistical significance was not reached for the reductions in DBP. In the OL arm, the mean changes from baseline at Week 24 were -3.10% (SE 0.22%) for HbA_{1c}, -1.93 kg (SE 0.44 kg) for body weight, -3.8 mmHg (SE 1.2 mmHg) for SBP, and -1.5 mmHg (SE 0.8 mmHg) for DBP.

Other analysed endpoints – FPG, waist circumference, the pre-defined composite endpoint (change in HbA_{1c}, BP, and body weight), relative response, treat-to-target response, and use of rescue medication – supported the findings for the primary and key secondary endpoints regarding the effect of the empagliflozin treatment (both doses) compared with placebo.

For most endpoints, the exploratory comparison of both empagliflozin doses vs. sitagliptin provided a larger treatment effect of empagliflozin. Treatment with empagliflozin 25 mg showed a numerically greater reduction in HbA_{1c} than treatment with sitagliptin; the reduction in HbA_{1c} for treatment with empagliflozin 10 mg was almost identical to that for sitagliptin. Treatment with both empagliflozin 10 mg and 25 mg reduced body weight and BP compared with sitagliptin treatment.

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Efficacy results (cont.)

Table 1: Change from baseline at Week 24 in primary and key secondary endpoints – full analysis set, last observation carried forward

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Sitagliptin 100mg
HbA_{1c} [%]				
Baseline mean (SE)	7.91 (0.05)	7.87 (0.06)	7.86 (0.06)	7.85 (0.05)
Adj. mean diff. to plac. (SE)[1]		-0.74 (0.07)	-0.85 (0.07)	-0.73 (0.07)
confidence interval (CI)[2]		(-0.90,-0.57)	(-1.01,-0.69)	(-0.88,-0.59)
p-value		<0.0001	<0.0001	
Body weight [kg]				
Baseline mean (SE)	78.23 (1.32)	78.35 (1.25)	77.80 (1.20)	79.31 (1.37)
Adj. mean diff. to plac. (SE)[1]		-1.93 (0.24)	-2.15 (0.24)	0.52 (0.25)
CI[2]		(-2.48,-1.38)	(-2.70,-1.60)	(0.04,1.00)
p-value		<0.0001	<0.0001	
SBP [mmHg] (SE)				
Baseline mean (SE)	130.4 (1.1)	133.0 (1.1)	129.9 (1.2)	132.5 (1.1)
Adj. mean diff. to plac. (SE)[1]		-2.6 (1.1)	-3.4 (1.1)	0.8 (1.2)
CI[2]		(-5.2,0.0)	(-6.0,-0.9)	(-1.4,3.1)
p-value		0.0231	0.0028	
DBP [mmHg]				
Baseline mean (SE)	78.9 (0.6)	79.2 (0.6)	78.3 (0.6)	80.1 (0.7)
Adj. mean diff. to plac. (SE)[1]		-0.6 (0.7)	-1.5 (0.7)	1.1 (0.7)
CI[2]		(-2.1,0.9)	(-3.0,0.0)	(-0.2,2.5)
p-value		0.3987	0.0296	

[*1] 'Adj. mean diff. to plac.' stands for 'Adjusted mean difference to placebo'
[2] 97.5% CI for empagliflozin 10 mg and for empagliflozin 25 mg, 95% CI for sitagliptin

Safety results:

The mean exposure to randomised treatment was: 163.2 days (SD 30.2 days) in the empagliflozin 10 mg group, 163.8 days (SD 29.3 days) in the empagliflozin 25 mg group, 164.3 days (SD 28.1 days) in the sitagliptin group, and 154.0 days (SD 42.0 days) in the placebo group. The mean exposure in the OL arm was 164.7 days (SD 29.0 days).

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Safety results (cont.):

The frequency of patients with treatment-emergent adverse events was: 54.9% in the empagliflozin 10 mg group, 60.5% in the empagliflozin 25 mg group, 53.4% in the sitagliptin group, and 61.1% in the placebo group. The highest frequency of adverse events was reported for the MedDRA system-organ class 'infections and infestations': 26.8% in the empagliflozin 10 mg group, 23.3% in the empagliflozin 25 mg group, 20.2% in the sitagliptin group, and 22.7% in the placebo group. Adverse events of severe intensity were reported for 8 patients (3.6%) in the empagliflozin 10 mg group, 7 patients (3.1%) in the empagliflozin 25 mg group, 5 patients (2.2%) in the sitagliptin group, and 4 patients (1.7%) in the placebo group.

Drug-related adverse events (as assessed by the investigator) were reported for 12.1% patients in the empagliflozin 10 mg group, 17.5% patients in the empagliflozin 25 mg group, 8.5% patients in the sitagliptin group, and 7.4% patients in the placebo group. There was no specific imbalance for single preferred terms across treatment groups.

The frequencies of patients with adverse events leading to premature discontinuation of trial medication were: 3.5% in the placebo group, 0.9% in the empagliflozin 10 mg group, 1.8% in the empagliflozin 25 mg group, 2.2% in the sitagliptin group.

Serious adverse events were reported for 8 patients (3.6%) in the empagliflozin 10 mg group, 5 patients (2.2%) in the empagliflozin 25 mg group, 6 patients (2.7%) in the sitagliptin group, and 6 patients (2.6%) on placebo. There was no specific trend for single preferred terms across treatment groups. One patient in the placebo group died during the study (myocardial infarction).

Hypoglycaemic events were reported at low frequencies in all randomised treatment groups; overall, 4 events were confirmed (1 patient / group). All episodes were of mild intensity. The mean changes from baseline in creatinine values at Week 24 and in estimated glomerular filtration rate (eGFR MDRD) in the randomised groups were small and comparable across treatment groups. One patient in the empagliflozin 10 mg group was reported with acute renal failure, a ≥2-fold increase from baseline in creatinine values and creatinine greater than upper limit normal and was discontinued from trial medication. One patient in the empagliflozin 25 mg group had laboratory values consistent with a potential Hy's law case. Drug-induced liver toxicity was ruled out after a careful assessment of the information available for this patient.

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Safety results (cont.):

Urinary tract infections were reported by 15 patients (6.7%) in the empagliflozin 10 mg group, 12 patients (5.4%) in the empagliflozin 25 mg group, 11 patients (4.9%) in the sitagliptin group, and 12 patients (5.2%) in the placebo group. Genital infections were reported by 7 patients (3.1%) in the empagliflozin 10 mg group, 9 patients (4.0%) in the empagliflozin 25 mg group, 2 patients (0.9%) in the sitagliptin group, and no patient in the placebo group.

In the OL arm, the overall frequency of adverse events was 64.4%. The highest frequency of adverse events was reported for the MedDRA system-organ class 'metabolism and nutrition disorders' (27.6%). One patient (1.1%) reported 1 adverse event of severe intensity. Drug-related adverse events (as assessed by the investigator) were reported by 12.6% patients. The frequency of adverse events leading to premature discontinuation of trial medication was 3.4%. Serious adverse events were reported by 3 patients (3.4%). There were no confirmed hypoglycaemic events. At Week 24, mean changes from baseline in creatinine values and in eGFR MDRD were small. Three patients (3.4%) reported urinary tract infections. One patient (1.1%) reported 1 genital infection.

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 24 weeks of treatment. Mean haematocrit values decreased from baseline to last value on treatment with placebo and sitagliptin but increased with empagliflozin 10 mg and empagliflozin 25 mg. A decrease in uric acid was noted in the empagliflozin groups compared with placebo or sitagliptin. When comparing the empagliflozin groups with the placebo group, a numerical increase in mean absolute change from baseline was observed in HDL cholesterol, with no major changes in LDL/HDL cholesterol ratio. Pulse rate changes were overall small across groups and did not increase under empagliflozin treatment.

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Conclusions:

Treatment with empagliflozin 10 mg and empagliflozin 25 mg once daily over 24 weeks as monotherapy was superior to placebo in reducing HbA_{1c} levels, body weight, and SBP in patients with type 2 diabetes and insufficient glycaemic control. For DBP, the reductions seen with empagliflozin treatment did not reach statistical significance. The reductions in HbA_{1c} levels, body weight, and BP for empagliflozin treatment were numerically greater than those seen for sitagliptin treatment. Generally, both empagliflozin doses were well tolerated and showed safety profiles similar to placebo, with the exception of reported genital infections (higher frequencies for empagliflozin treatment). The frequencies of patients reported with hypoglycaemic events or urinary tract infections were overall low and comparable across treatment groups.

Trial Synopsis – Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results of the trial.

Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	presented in
Disposition of patients	Table 15.1.1: 1

Table 15.1.1: 1 Disposition of patients - screened patients set

	Placebo N (%)	Empa 10mg N (%)	Empa 25mg N (%)	Sitagliptin N (%)	Total Rand. N (%)	Empa 25mg OL N (%)
Screened						
Started placebo run-in						
Not entered						
Entered	228	224	224	223	899	87
Not treated	0	0	0	0	0	0
Treated	228 (100.0)	224 (100.0)	224 (100.0)	223 (100.0)	899 (100.0)	87 (100.0)
Not prematurely discontinued from trial medication	187 (82.0)	206 (92.0)	204 (91.1)	206 (92.4)	803 (89.3)	78 (89.7)
Prematurely discontinued from trial medication	41 (18.0)	18 (8.0)	20 (8.9)	17 (7.6)	96 (10.7)	9 (10.3)
Adverse event	8 (3.5)	2 (0.9)	4 (1.8)	6 (2.7)	20 (2.2)	3 (3.4)
Worsening of disease under study	0	0	0	0	0	1 (1.1)
Worsening of other pre-existing disease	0	1 (0.4)	1 (0.4)	0	2 (0.2)	0
Other adverse event	8 (3.5)	1 (0.4)	3 (1.3)	6 (2.7)	18 (2.0)	2 (2.3)
Lack of efficacy	1 (0.4)	0	0	0	1 (0.1)	0
Non compliant with protocol	3 (1.3)	2 (0.9)	2 (0.9)	0	7 (0.8)	1 (1.1)
Lost to follow-up	12 (5.3)	5 (2.2)	6 (2.7)	3 (1.3)	26 (2.9)	0
Patient refusal to continue, not due to AE	12 (5.3)	7 (3.1)	6 (2.7)	5 (2.2)	30 (3.3)	3 (3.4)
Other	5 (2.2)	2 (0.9)	2 (0.9)	3 (1.3)	12 (1.3)	2 (2.3)
Continued in extension study	136 (59.6)	165 (73.7)	159 (71.0)	155 (69.5)	615 (68.4)	0
Did not continue in extension study	92 (40.4)	59 (26.3)	65 (29.0)	68 (30.5)	284 (31.6)	87 (100.0)
Ineligible	12 (5.3)	5 (2.2)	6 (2.7)	5 (2.2)	28 (3.1)	54 (62.1)
Tolerability issues	4 (1.8)	2 (0.9)	3 (1.3)	0	9 (1.0)	0
Other	76 (33.3)	52 (23.2)	56 (25.0)	63 (28.3)	247 (27.5)	33 (37.9)

'Entered' means randomised or assigned to open-label treatment.
Source data: Appendix 16.2.1, Listing 1

Table 15.1.1: 1 Disposition of patients - screened patients set

	Total N (%)
Screened	1616
Started placebo run-in	969
Not entered	630
Entered	986
Not treated	0
Treated	986 (100.0)
Not prematurely discontinued from trial medication	881 (89.4)
Prematurely discontinued from trial medication	105 (10.6)
Adverse event	23 (2.3)
Worsening of disease under study	1 (0.1)
Worsening of other pre-existing disease	2 (0.2)
Other adverse event	20 (2.0)
Lack of efficacy	1 (0.1)
Non compliant with protocol	8 (0.8)
Lost to follow-up	26 (2.6)
Patient refusal to continue, not due to AE	33 (3.3)
Other	14 (1.4)
Continued in extension study	615 (62.4)
Did not continue in extension study	371 (37.6)
Ineligible	82 (8.3)
Tolerability issues	9 (0.9)
Other	280 (28.4)

'Entered' means randomised or assigned to open-label treatment.
Source data: Appendix 16.2.1, Listing 1