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		Synopsis	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2010-018708-99	
BI Investigational Product: Empagliflozin (BI 10773)		**Page:** 1 of 8	
Report Date: 18 Aug 2014	**Trial No. / Doc. No.:** 1245.39 / c02836447	**Dates of Trial:** 15 Aug 2011 - 08 July 2013	**Date of Revision:** Not applicable

Title of Trial:	An open-label, phase II study to determine acute (after the first dose administration) and chronic (after 28 days of treatment) effects of the sodium-glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin (BI 10773) (25 mg once daily) on pre and postprandial glucose homeostasis in patients with IGT, type 2 diabetes mellitus and healthy subjects
Coordinating Investigator:	[redacted]
Trial Sites:	The study was conducted at 3 sites: • Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany • Azienda Ospedaliera Pisana - Dip. di Medicina Interna, Pisa, Italy • Univ. Klinik f. Innere Medizin, Graz, Austria
Publications:	Interim data with a data lock point of 19 March 2013 were published: Ferrannini E, Muscelli E, Frascerra S, et al. J Clin Invest. 2014;124(2):499-508.
Clinical Phase:	II
Objectives:	The objective of the study was to investigate the acute and chronic effect of empagliflozin on fasting and postprandial glucose homeostasis in patients with impaired glucose tolerance (IGT) or with type 2 diabetes mellitus (T2DM) with and without metformin and the acute effect of empagliflozin on fasting and postprandial glucose homeostasis in healthy subjects.
Methodology:	This was an open-label, multi-national, single arm study designed to compare metabolic parameters after a single dose and after 4 weeks of study treatment to baseline in patients with T2DM or IGT, and after a single dose to baseline in healthy subjects. For healthy subjects a single dose of placebo was given followed by a single dose of empagliflozin 25 mg on the next day. For patients (T2DM or IGT), a 1-week placebo run-in period preceded the 4-week treatment phase with empagliflozin 25 mg.

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No. of Subjects:

Planned: Entered: ≥90 (at least 78 patients [n=12 with IGT, n=33 drug-naïve T2DM patients, and n=33 T2DM patients on metformin] and at least 12 healthy subjects)

Actual: Enrolled: 194

Entered placebo run-in phase: 95

Entered treatment phase: 91

Drug naïve T2DM patients (T2DM naïve):
Empagliflozin 25 mg once daily for 28 days:

Entered: 32 Treated: 32 Analysed (for primary endpoint): Day 1: 32; Day 28: 32

T2DM patients on metformin (T2DM met.):
Empagliflozin 25 mg once daily for 28 days:

Entered: 34 Treated: 34 Analysed (for primary endpoint): 34 Day 1: 34; Day 28: 33

IGT patients (IGT): Empagliflozin 25 mg once daily for 28 days:

Entered: 13 Treated: 13 Analysed (for primary endpoint): 13 Day 1: 13; Day 28: 13

Healthy subjects (Healthy sub.): Empagliflozin 25 mg, single dose:

Entered: 12 Treated: 12 Analysed (for primary endpoint): Day 1: 12

Diagnosis:

- Patients diagnosed with IGT according to American Diabetes Association (ADA) guidelines, or
- drug naïve T2DM patients: patients diagnosed with T2DM not treated with any antihyperglycemic therapy for 12 weeks prior to the study , or
- T2DM patients on metformin: patients diagnosed with T2DM on stable dose of metformin of at least 1500 mg per day, for 12 weeks prior to the study, or
- healthy subjects as characterised by inclusion criteria.

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Main Criteria for Inclusion:	Patients (IGT or T2DM): aged ≥18 years, body mass index ≥20 and ≤40 kg/m^2, on stable antihypertensive medication (if any), with HbA1c <6.5 (IGT) or ≥6.5% and ≤10.5% (T2DM). Healthy subjects: aged ≥45 and ≤55 years, body mass index ≥30 and ≤40 kg/m^2, with HbA1c <6.5% and confirmed normal glucose tolerance.
BI Investigational Product:	Empagliflozin
Dose:	25 mg once daily
Mode of Admin.:	Oral, tablet
Batch No.:	B093000531
Comparator Product:	Placebo matching empagliflozin (given during open-label placebo run-in phase only)
Dose:	Not applicable
Mode of Admin.:	Oral, tablet
Batch No.:	B093000525
Duration of Treatment:	4 weeks for IGT and T2DM patients Single dose for healthy subjects
Criteria for Evaluation:	
Efficacy:	The primary endpoints were: • the change in fasting plasma glucose (FPG) from baseline to the first administration of study medication (all subjects) and to 28 days of treatment (IGT and T2DM patients), and • the change in 0 to 5 hour incremental area under the curve post-prandial glucose (PPG iAUC 5h) from baseline to the first administration of study medication (all subjects) and to 28 days of treatment (IGT and T2DM patients). The secondary endpoint was the change in rate of endogenous glucose production (EGP) from baseline to the first administration of study medication (all subjects) and to 28 days of treatment (IGT and T2DM patients). Variables were fasting EGP, EGP AUC 5h, and EGP iAUC 5h.

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Criteria for Evaluation: Safety:	Adverse events (AEs): serious and most frequent (>5.0 % of subjects in any diagnosis group) non-serious AEs
Statistical Methods:	Exploratory statistics only, consisting of descriptive and graphical analysis. Primary analysis: ANCOVA model and other exploratory analyses as deemed necessary are provided but all reported p-values are regarded as descriptive p-values and adjustment for multiple comparisons of endpoints between populations are not necessary.

SUMMARY - CONCLUSIONS:

Trial Subjects:

Of the 194 patients enrolled, 95 entered the open-label placebo run-in period, and 91 patients were treated with empagliflozin. One patient (in the T2DM met. group) was prematurely discontinued from the trial due to an AE.

Patients in this trial were predominantly male (T2DM naïve: 65.6%; T2DM met.:70.6%; IGT: 61.5%; Healthy sub.: 83.3%). All patients were white Europeans. The mean (SD) age was 60.1 (7.0) years for T2DM naïve patients, 63.3 (6.5) years for T2DM met. patients, 50.8 (9.8) years for IGT patients, and 47.7 (2.3) years for Healthy subjects. The mean (SD) BMI was 32.27 (4.52) kg/m^2 for T2DM naïve patients, 31.04 (4.68) kg/m^2 for T2DM met. patients, 34.15 (4.11) kg/m^2 for IGT patients, and 33.83 (2.90) kg/m^2 for Healthy subjects. The mean (SD) estimated glomerular filtration rate (eGFR) was 84.35 (15.45) $mL/min/1.73m^2$ for T2DM naïve patients, 86.60 (14.24) $mL/min/1.73m^2$ for T2DM met. patients, 87.68 (13.25) $mL/min/1.73m^2$ for IGT patients, and 85.80 (13.44) $mL/min/1.73m^2$ for Healthy subjects.

Mean FPG at baseline was 8.23 mmol/L for T2DM naïve patients, 9.09 mmol/L for T2DM met. patients, 5.72 mmol/L for IGT patients, and 5.89 mmol/L for Healthy subjects. Mean PPG incremental area under the curve from 0 to 5 h post meal (iAUC 5h) at baseline was 17.74 g/dL/h for T2DM naïve patients, 21.55 g/dL/h for T2DM met. patients, 11.37 g/dL/h for IGT patients, and 7.61 g/dL/h for Healthy subjects.

Efficacy Results:

Primary endpoints:

For T2DM naïve patients, the adjusted mean change in **FPG** was 0.20 mmol/L from baseline to Day 1 (after the first dose of empagliflozin) and -1.02 mmol/L from baseline to Day 28 (after 4 weeks of treatment). For T2DM met. patients, the adjusted mean change was 0.39 mmol/L from baseline to Day 1 and -0.79 mmol/L from baseline to Day 28.

Efficacy Results (continued):

For IGT patients, the adjusted mean change was -0.96 mmol/L from baseline to Day 1 and -0.81 mmol/L from baseline to Day 28. For Healthy subjects, the adjusted mean change was -0.47 mmol/L from baseline to Day 1.

The adjusted mean (SE) difference in change from baseline to Day 1 between T2DM met. and T2DM naïve patients was 0.19 (0.18) mmol/L (95% confidence interval [CI]: −0.16, 0.55; p-value: 0.2790). The adjusted mean (SE) difference in change from baseline to Day 28 between T2DM met. and T2DM naïve patients was 0.23 (0.20) mmol/L (95% CI: -0.16, 0.62; p-value: 0.2438).

Table 1 Adjusted mean change in FPG (mmol/L) at Day 1 and Week 4 – Treated set

	T2DM naïve	T2DM met.	IGT	Healthy subjects
Subjects	32	34	13	12
Analysed	32	34[1]	13	12
Mean at baseline (SE)	8.23 (0.23)	9.09 (0.29)	5.72 (0.13)	5.89 (0.12)
Mean at Day 1 (SE)	8.36 (0.21)	9.34 (0.29)	5.77 (0.11)	5.89 (0.11)
Mean at Day 28 (SE)	7.20 (0.11)	7.99 (0.24)	5.47 (0.13)	n.a.
Change from baseline to Day 1				
Mean (SE)	0.13 (0.11)	0.25 (0.14)	0.05 (0.10)	0.00 (0.08)
Adj.[2] mean (SE)	0.20 (0.12)	0.39 (0.13)	−0.96 (0.86)	−0.47 (0.97)
Change from baseline to Day 28				
Mean (SE)	−1.03 (0.18)	−1.19 (0.21)	−0.25 (0.09)	n.a.
Adj.[3] mean (SE)	−1.02 (0.13)	−0.79 (0.15)	−0.81 (1.12)	n.a.

SE= standard error; adj. = adjusted; n.a = not available (Healthy subjects received only one dose at Day 1)

[1] For Day 28 analysis: 33 patients

[2] ANCOVA model for Day 1 includes baseline FPG (p=0.1045) as linear covariate(s) and diagnosis group (p=0.9189), baseline FPG by diagnosis group interaction (p=0.7441) as fixed effect(s)

[3] ANCOVA model for Day 28 includes baseline FPG (p=0.0056) as linear covariate(s) and diagnosis group (p=0.1548), baseline FPG by diagnosis group interaction (p=0.1064) as fixed effect(s).

Efficacy Results (continued):

For T2DM naïve patients, the adjusted mean change in **PPG iAUC 5h** was -1.94 g/dL/h from baseline to Day 1 and -0.71 g/dL/h from baseline to Day 28. For T2DM met. patients, the adjusted mean change was -3.52 g/dL/h from baseline to Day 1 and −0.40 g/dL/h from baseline to Day 28. For IGT patients, the adjusted mean change was -5.49 g/dL/h from baseline to Day 1 and -7.31 g/dL/h from baseline to Day 28. For Healthy subjects, the adjusted mean change was -9.20 g/dL/h from baseline to Day 1.

The adjusted mean (SE) difference in change from baseline to Day 1 between T2DM met. and T2DM naïve patients was -1.58 (0.81) g/dL/h (95% CI: −3.20, 0.04; p-value: 0.0552). The adjusted mean (SE) difference in change from baseline to Day 28 between T2DM met. and T2DM naïve patients was 0.31 (0.99) g/dL/h (95% CI: -1.66, 2.27; p-value: 0.7561).

Table 2 Adjusted mean change in PPG iAUC 5h (g/dL/h) at Day 1 and Week 4 – Treated set

	T2DM naïve	T2DM met.	IGT	Healthy sub.
Subjects	32	34	13	12
Analysed	32	34[1]	13	11
Mean at baseline (SE)	17.74 (1.17)	21.55 (1.22)	11.37 (0.77)	7.61 (0.71)
Mean at Day 1 (SE)	15.60 (0.96)	16.10 (0.95)	8.60 (0.77)	6.60 (0.50)
Mean at Day 28 (SE)	17.23 (0.94)	19.46 (0.99)	11.00 (0.56)	n.a.
Change from baseline to Day 1				
Mean (SE)	−2.14 (0.54)	−5.45 (0.82)	−2.77 (0.75)	−1.01 (0.79)
Adj.[2] mean (SE)	−1.94 (0.53)	−3.52 (0.61)	−5.49 (1.95)	−9.20 (3.91)
Change from baseline to Day 28				
Mean (SE)	−0.51 (0.74)	−2.05 (1.00)	−0.37 (0.95)	n.a
Adj.[3] mean (SE)	−0.71 (0.67)	−0.40 (0.72)	−7.31 (2.91)	n.a

SE= standard error; adj. = adjusted; n.a = not available (Healthy subjects received only one dose at Day 1)

[1] For Day 28 analysis: 33 patients

[2] ANCOVA model for Day 1 baseline PPG iAUC 5h (p=0.0002) as linear covariate(s) and diagnosis group (p=0.8632), baseline PPG iAUC 5h by diagnosis group interaction (p=0.3138) as fixed effect(s).

[3] ANCOVA model for Day 28 includes baseline PPG iAUC 5h (p<0.0001) as linear covariate(s) and diagnosis group (p=0.5016), baseline PPG iAUC 5h by diagnosis group interaction (p=0.2583) as fixed effect(s).

Efficacy Results (continued):

Secondary endpoints:

For T2DM naïve patients, mean (SE) **fasting EGP** at baseline was 12.32 (0.46) µmol/kg fat free mass (FFM)/min; the adjusted mean (SE) change was 4.21 (0.45) µmol/kgFFM/min from baseline to Day 1 and 2.79 (0.71) µmol/kgFFM/min from baseline to Day 28. For T2DM met. patients, mean (SE) at baseline was 16.12 (0.43) µmol/kgFFM/min; the adjusted mean (SE) change was 4.51 (0.60) µmol/kgFFM/min from baseline to Day 1 and 4.63 (0.86) µmol/kgFFM/min from baseline to Day 28. For IGT patients, mean (SE) at baseline was 11.23 (0.67) µmol/kgFFM/min; the adjusted mean (SE) change was 3.28 (0.89) µmol/kgFFM/min from baseline to Day 1 and 1.47 (1.44) µmol/kgFFM/min from baseline to Day 28. For Healthy subjects, mean (SE) at baseline was 11.03 (0.71) µmol/kgFFM/min; the adjusted mean (SE) change was 1.10 (0.97) µmol/kgFFM/min from baseline to Day 1.

The adjusted mean (SE) difference in change from baseline to Day 1 between T2DM met. and T2DM naïve patients was 0.30 (0.75) µmol/kgFFM/min (95% CI: −1.19, 1.79; p-value: 0.6931). The adjusted mean (SE) difference in change from baseline to Day 28 between T2DM met. and T2DM naïve patients was 1.84 (1.12) µmol/kgFFM/min (95% CI: −0.38, 4.07; p-value: 0.1028).

For T2DM naïve patients, mean (SE) **EGP AUC 5h** at baseline was 34.08 (1.44) g; the adjusted mean (SE) change was 3.28 (1.80) g from baseline to Day 1 and 1.89 (1.35) g from baseline to Day 28. For T2DM met. patients, mean (SE) at baseline was 33.89 (1.28) g; the adjusted mean (SE) change was 8.76 (1.77) g from baseline to Day 1 and 5.02 (1.33) g from baseline to Day 28. For IGT patients, mean (SE) at baseline was 38.03 (1.95) g; the adjusted mean (SE) change was 3.70 (2.73) g from baseline to Day 1 and 3.14 (2.35) g from baseline to Day 28. For Healthy subjects, mean (SE) at baseline was 51.32 (5.07) g; the adjusted mean (SE) change was 9.22 (3.94) g from baseline to Day 1.

The adjusted mean (SE) difference in change from baseline to Day 1 between T2DM met. and T2DM naïve patients was 5.48 (2.52) g (95% CI: 0.47,10.50; p-value: 0.0326). The adjusted mean (SE) difference in change from baseline to Day 28 between T2DM met. and T2DM naïve patients was 3.13 (1.89) g (95% CI: −0.64, 6.90; p-value: 0.1024).

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Efficacy Results (continued):

For T2DM naïve patients, mean (SE) **EGP iAUC 5h** at baseline was −6.06 (1.71) g; the adjusted mean (SE) change was −8.52 (1.79) g from baseline to Day 1 and −6.95 (2.26) g from baseline to Day 28. For T2DM met. patients, mean (SE) at baseline was −18.73 (1.99) g; the adjusted mean (SE) change was −7.22 (2.33) g from baseline to Day 1 and −10.63 (2.50) g from baseline to Day 28. For IGT patients, mean (SE) at baseline was −0.24 (2.33) g; the adjusted mean (SE) change was −3.75 (3.82)g from baseline to Day 1 and −0.49 (5.22) g from baseline to Day 28. For Healthy subjects, mean (SE) at baseline was 9.90 (4.52) g; the adjusted mean (SE) change was 1.28 (4.80) g from baseline to Day 1.

The adjusted mean (SE) difference in change from baseline to Day 1 between T2DM met. and T2DM naïve patients was 1.31 (2.93) g (95% CI: −4.53, 7.14; p-value: 0.6576). The adjusted mean (SE) difference in change from baseline to Day 28 between T2DM met. and T2DM naïve patients was −3.68 (3.38) g (95% CI: −10.41, 3.05; p-value: 0.2795).

Safety Results:

Only one patient in this trial experienced a serious AE; myocardial infarction in a 55 year old male T2DM met. patient. The event led to study discontinuation, was considered not related to study treatment, and the patient recovered from the event. No subject died in this trial.

Non-serious AEs were reported for 14 patients (43.8%) in the T2DM naïve group, 6 patients (17.6%) in the T2DM met. group, 4 patients (30.8%) in the IGT group, and 1 (8.3%) Healthy subject. The most common AE was nasapharyngitis, which was reported in 2 T2DM naïve patients and 1 subject each in the other groups.

Conclusions:

Four weeks of treatment with empagliflozin led to a reduction in FPG and PPG iAUC 5h with a compensatory increase in EGP in T2DM and IGT patients. The treatment with empagliflozin was well tolerated in all diagnosis groups.