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.:** 2009-013668-38	**Synopsis No.:**
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 10	
Module:		**Volume:**	
Report date: 11 JAN 2013	**Trial No. / U No.:** 1245.33 / U12-3817-01	**Date of trial:** 11 Nov 2009 – 09 May 2012	**Date of revision:** Not applicable

Title of trial:	A phase IIb, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 10773 (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic patients receiving treatment with basal insulin (glargine, detemir, or NPH insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre Study, c f. Appendix 16.1.4
Publication (reference):	Data of this study have not been published.
Clinical phase:	IIb
Objectives:	To investigate the safety, efficacy, tolerability, and pharmacokinetics of empagliflozin (10 mg or 25 mg, administered orally, once daily) compared to placebo given for 78 weeks in combination with background basal insulin therapy (glargine, detemir, or NPH insulin only) at a fixed dose for 18 weeks (except for rescue therapy), and at an adjustable dose for 60 weeks with or without concomitant metformin and/or sulfonylurea therapy, in patients with type 2 diabetes mellitus (T2DM) with insufficient glycemic control.
Methodology:	Randomized, double-blind, placebo-controlled, parallel group comparison. Randomization was stratified by glycosylated hemoglobin A_{1c} (HbA_{1c}) at screening. A 2-week open-label placebo run-in period preceded randomization.

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No. of subjects:	
planned:	Enrolled: 985 (screened) Entered: 450 (150 per treatment)
actual:	Enrolled: 826 (screened) Started placebo run-in: 532 Randomized (total): 494 Empagliflozin 10 mg Entered: 169; treated: 169; analyzed (for primary endpoint): 132 Empagliflozin 25 mg Entered: 155; treated: 155; analyzed (for primary endpoint): 117 Placebo Entered: 170; treated: 170; analyzed (for primary endpoint): 125
Diagnosis and main criteria for inclusion:	Patients ≥18 years with T2DM with HbA_{1c} >7% and ≤10.0% and on basal insulin (glargine or detemir insulin of ≥20 IU/day or NPH insulin ≥14 IU/day) with or without concomitant metformin and / or sulfonylurea therapy
Test product:	Empagliflozin (BI 10773) 5 mg
dose:	10 mg (2 x 5-mg tablets) once daily
mode of admin.:	Oral
batch no.:	B093000188, B093000526, B093000527
Test product:	Empagliflozin (BI 10773) 25 mg
dose:	25 mg once daily
mode of admin.:	Oral
batch no.:	B093000196, B093000531
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	oral
batch no.:	B083000063, B093000144, B093000525
Duration of treatment:	78 weeks (2 week placebo run-in; 78-week treatment period; 4-week follow up)

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Criteria for evaluation:

Efficacy / clinical pharmacology:	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 dose of basal insulin dose after 78 weeks of treatment and change from baseline in HbA_{1c} after 78 weeks of treatment (endpoints introduced with a protocol amendment).
Safety:	Adverse events (AEs), including hypoglycemic events, protocol-specified significant AEs (urinary tract infections [UTI], genital infections [introduced in the TSAP], Clinical Event Committee-adjudicated cardiovascular events, and other adverse events of special interest [AESIs]). Change from baseline in clinical laboratory assessments (including lipid parameters to Week 78), and vital signs.
Statistical methods:	Testing of superiority of each dose of empagliflozin versus placebo with an analysis of covariance for HbA_{1c} change from baseline after 18 weeks with factor for treatment and baseline HbA_{1c} as covariate. To maintain the overall type-I (alpha) at 5%, the two treatment comparisons (empagliflozin 10 mg vs. placebo and empagliflozin 25 mg vs. placebo) were both tested at the significance level of 0.025 which is half of the overall alpha of 0.05. A hierarchical testing approach was applied to each of the two dose comparisons to placebo for key secondary endpoints of change from baseline in dose of basal insulin and HbA_{1c} after 78 weeks of treatment. The key secondary endpoints analyzed at 78 weeks were intended to show decreased use of insulin (superiority) accompanied by similar levels of HbA_{1c} (non-inferiority) or even greater decrease in HbA_{1c} (superiority) compared with placebo. Exploratory statistics were used to analyze secondary endpoints and safety parameters.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

This trial screened 826 patients in 97 centers in 7 countries in Asia, Europe, and North America. Of the patients screened, 532 started the placebo run-in period. Overall, 494 patients were randomized to double-blind treatment with either empagliflozin 10 mg (169 patients), empagliflozin 25 mg (155 patients), or placebo (170 patients). The main reason for not being randomized in this trial was inclusion/exclusion criteria not met. Randomization was stratified by HbA_{1c} at screening; approximately 60% of patients in each treatment group had an HbA_{1c} <8.5% at screening.

Demographic data were generally balanced among the 3 treatment groups. More than half of the patients were male, most patients (≥66.5%) were White, and approximately 20% of patients were Asian. The mean age of patients was similar across the 3 treatment groups (approximately 59 years). The mean baseline body mass index (BMI) was also similar across the 3 treatment and the majority of patients had normal renal function or mild renal impairment at baseline.

Most baseline efficacy characteristics were balanced across the treatment groups. The mean HbA_{1c} of patients was 8.27% in both the empagliflozin 10 mg and 25 mg groups and was 8.18% in the placebo group. Mean FPG levels were slightly lower at baseline in the empagliflozin 10 mg group (138.4 mg/dL) compared with the empagliflozin 25 mg group (146.4 mg/dL) and the placebo group (142.1 mg/dL). As expected in this population using basal insulin, approximately 90% of the patients had a T2DM history of > 5 years. More than 75% of patients had a history of hypertension.

The primary endpoint in this study was the change from baseline in HbA_{1c} (%) after 18 weeks of treatment. The analysis of the primary endpoint showed both clinically meaningful and statistically significant ($p<0.0001$) reductions in HbA_{1c} with both doses of empagliflozin compared with placebo. The adjusted mean differences versus placebo were -0.56% in the empagliflozin 10 mg group (97.5% CI: -0.78, -0.33) and -0.70% in the empagliflozin 25 mg group (97.5% CI: -0.93, -0.47). All sensitivity analyses of the primary endpoint confirmed these results. An analysis of HbA_{1c} change over time showed that the treatment effects of both doses of empagliflozin increased up to Week 12 and were sustained thereafter.

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Efficacy / clinical pharmacology result (continued)s:

For the key secondary endpoint of basal insulin dose, the adjusted mean differences from placebo at Week 78 were -6.66 IU in the empagliflozin 10 mg group (97.5% CI: -11.56, -1.77) and -5.92 IU in the empagliflozin 25 mg group (97.5% CI: -11.00, -0.85). Superiority vs. placebo was achieved and the robustness of these results was confirmed by sensitivity analyses.

After 78 weeks of treatment, there were also clinically meaningful and statistically significant ($p \leq 0.0001$) reductions in HbA_{1c} with both doses of empagliflozin versus placebo. The adjusted mean differences versus placebo were -0.46% in the empagliflozin 10 mg group (97.5% CI: -0.73, -0.19) and -0.62% in the empagliflozin 25 mg group (97.5% CI: -0.90, -0.34). These results were confirmed by sensitivity analyses.

A greater proportions of patients treated with empagliflozin 10 mg and 25 mg vs. placebo achieved absolute (HbA_{1c} levels of <7.0% or <6.5%) and relative efficacy responses (≥0.5% reduction in HbA_{1c}) relative to baseline after both 18 and 78 weeks of treatment.

In the first part of the study, up to Week 18, the insulin dose was supposed to remain stable. During this period FPG levels increased in the placebo group and decreased in the empagliflozin group: the placebo corrected difference at Week 18 was -28.40 (95% CI: -37.54, -19.27) in the empagliflozin 10 mg group and -34.21 (95% CI: -43.67,-24.76) in the empagliflozin 25 mg group. During the second part of the trial it was recommended that patient insulin dose be titrated to achieve FPG levels <110 mg/dL.

As a result of the titration, FPG levels decreased in the placebo group through Week 78 (adjusted mean change from baseline of -5.48 mg/dL) compared to the result at Week 18 (adjusted mean change from baseline of 11.15 mg/dL). In the empagliflozin groups, the FPG lowering effect was maintained through Week 78. Despite the decrease in FPG in the placebo group, significant differences in FPG levels were observed at Week 78 of -5.03 (95 CI: -15.01, 4.94) in the empagliflozin 10 mg group and -11.95 (95% CI: -22.24, -1.67) in the empagliflozin 25 mg group.

Clinically meaningful reductions in MDG were also reported at Week 18 and Week 78 for both doses of empagliflozin in the subset of patients for whom data were available.

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Efficacy / clinical pharmacology result (continued)s:	Analyses of weight response (>5% reduction in weight) relative to baseline after 18 and 78 weeks of treatment showed that greater proportions of patients treated with empagliflozin 10 mg and 25 mg achieved these targets compared with patients receiving placebo. In addition, there were reductions in body weight with both doses of empagliflozin at Week 18 that were sustained through Week 78; the difference versus placebo for the adjusted mean change in body weight from baseline at Week 78 -3.63 kg (95% CI: -5.81, -1.46) for the empagliflozin 10 mg group and -3.12 kg (95% CI: -5.39, -0.85) for the empagliflozin 25 mg group.. These reductions in weight were also reflected in reductions in BMI and waist circumference. There were clinically meaningful reductions in both SBP and DBP when comparing patients treated with empagliflozin 10 mg or 25 mg versus placebo after 18 weeks of treatment and these changes were sustained through Week 78. At Week 78, the difference versus placebo for the adjusted mean change in SBP from baseline was -4.2 mmHg (95% CI: -7.0, -1.3) for the empagliflozin 10 mg group and -2.4 mmHg (95% CI: -5.4, 0.5) for the empagliflozin 25 mg group. Empagliflozin trough concentrations were similar within each dose group on Days 43, 85, and 127 indicating that steady-state concentrations of empagliflozin were maintained during the course of the study. The increase in empagliflozin exposure with dose was roughly proportional with an increase in dose from 10 mg to 25 mg.
Safety results:	A total of 494 patients were treated with study medication and included in the safety analysis. The treated set consisted of 169 patients who received 10 mg empagliflozin, 155 patients who received 25 mg empagliflozin, and 170 patients who received placebo. The mean (SD) exposure to randomized study medication was 464.4 (167.9) days in the empagliflozin 10 mg group, 447.0 (183.4) days in the empagliflozin 25 mg group, and 434.6 (188.0) days in the placebo group. The median exposure to randomized study medication was 546.0 days (78 weeks) in the empagliflozin 10 mg and 25 mg groups and 545.0 days in the placebo group. The total exposure was 214.9 patient years for patients in the empagliflozin 10 mg group, 189.7 patient years for patients in the empagliflozin 25 mg group, and 202.3 patient years for patients in the placebo group.

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Safety results (continued):

Overall, the frequency of patients with adverse events on treatment was similar in the 3 treatment groups: 84.6% of patients in the empagliflozin 10 mg group, 87.1% of patients in the empagliflozin 25 mg group, and 87.1% of patients in the placebo group. AEs were mostly of mild or moderate intensity and severe adverse events were reported for a minority of patients with a slightly higher frequency in the empagliflozin 25 mg group (14.2%) compared with the empagliflozin 10 mg (8.9%) and placebo (10.6%) groups. During the treatment period, the highest incidence of adverse events was reported for the MedDRA system organ class (SOC) 'infections and infestations' reported by a higher proportion of patients in the empagliflozin groups (10 mg: 49.1%, empagliflozin 25 mg: 45.8%) compared with the placebo group (42.9%). At Week 18, SOCs with the highest incidence of AEs included ‘metabolism and nutrition disorders’ (empagliflozin 10 mg: 26.0%, empagliflozin 25 mg: 30.3%, placebo: 24.7%) and ‘infections and infestations’ (empagliflozin 10 mg: 29.6%, empagliflozin 25 mg: 25.8%, placebo: 24.7%). The most common preferred term (PT) at Week 18 was hypoglycemia: empagliflozin 10 mg: 18.3%, empagliflozin 25 mg: 25.2%, placebo: 20.0%).

SAEs were reported by 28 patients in each group: 16.6% in the empagliflozin 10 mg group, 18.1% in the empagliflozin 25 mg group, and 16.5% in the placebo group. One patient in the placebo group died during the study (hemorrhagic stroke); no patient in either empagliflozin group died during the study. Serious coronary artery disease was reported for 4 patients (2 in the empagliflozin 10 mg group and 2 in the placebo group) and serious osteoarthritis was reported for 3 patients (2 in the empagliflozin 10 mg group and 1 in the empagliflozin 25 mg group); the remaining SAEs were reported for only 1 or 2 patients each.

Adverse events led to premature discontinuation of trial medication in 19 patients (11.2%) in the empagliflozin 10 mg group, 20 patients (12.9%) in the empagliflozin 25 mg group, and 13 patients (7.6%) in the placebo group. Most AEs leading to premature discontinuation of trial medication were reported for only 1 patient each.

The proportions of patients with adverse events considered to be drug-related by the investigator were higher in the empagliflozin 25 mg group compared with the empagliflozin 10 mg or the placebo group. Overall, very few other significant adverse events were reported in this study with proportions similar in the treatment groups.

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Safety results (continued):

For 19 patients (3.8% overall), cardiovascular events were confirmed by the CEC. One patient in the placebo group had a fatal event (hemorrhagic stroke in Patient [redacted]) and 18 patients (3.6% overall) had non-fatal cardiovascular events (6 in the empagliflozin 10 mg group, 7 in the empagliflozin 25 mg group, and 5 in the placebo group. In total, 8 patients (3 in the empagliflozin 10 mg group, 4 patients in the empagliflozin 25 mg group and 1 in the placebo group) were assessed as having a 4-MACE event.

Investigator-defined hypoglycemia events were reported for a comparable proportion of patients in the three treatment groups: 64 patients (37.9%) in the empagliflozin 10 mg group, 61 patients (39.4%) in the empagliflozin 25 mg group, and 64 patients (37.6%) in the placebo group. These results were consistent with those reported for confirmed hypoglycemic events. Two (1.3%) patients in the empagliflozin 25 mg group had confirmed hypoglycemia events that required assistance. In 1 of these patients in the empagliflozin 25 mg group the hypoglycemia event was also severe in intensity and required hospitalization.

MedDRA based searches for renal events identified 11 patients (6 in the empagliflozin 10 mg group, 3 in the empagliflozin 25 mg group, and 2 in the placebo group); 4 of these 11 patients had protocol-specified significant renal events (3 patients in the empagliflozin 10 mg group and 1 patient in the empagliflozin 25 mg group).

Further changes in markers of renal function (creatinine and eGFR) during the treatment phase were generally small and similar in the 3 treatment groups; for patients treated with empagliflozin the small decreases in eGFR returned to baseline after follow-up. Slight improvements in albuminuria and urine albumin/creatinine ratios were observed for the empagliflozin treatment groups. A few patients shifted across renal impairment categories (based on eGFR values) from baseline to end of treatment. Shifts occurred in both directions and with a similar frequency across treatment groups.

Fourteen patients (3 in the empagliflozin 10 mg group, 5 in the empagliflozin 25 mg group, and 6 in the placebo group) had hepatic AEs based on standardized MedDRA queries. No patient was confirmed to satisfy Hy´s law.

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Safety results (continued):

The overall frequency of UTIs was higher in the empagliflozin 10 mg (14.8%) and empagliflozin 25 mg groups (11.6%) compared with the placebo group (8.8%). UTI events were more frequently reported for female patients. Three UTI events were severe (1 in each treatment group) and 1 event the empagliflozin 25 mg group required hospitalization of the patient and 1 of the reported UTIs led to premature discontinuation of study medication (empagliflozin 25 mg group).

The overall frequency of genital infections was 7.7% in the empagliflozin 10 mg group, 5.2% in the empagliflozin 25 mg group and 1.8% in the placebo group. Two of the reported genital infections led to premature discontinuation of study medication (1 patient in the empagliflozin 10 mg group and 1 patient in the empagliflozin 25 mg group). Genital infections were reported with a similar incidence regardless of gender.

Overall, mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, urinalysis and plasma proteins were negligible after 18 and 78 weeks of treatment. Incidences of possibly clinically significant abnormalities were generally similar between the treatment groups and across the time points.

For hematocrit and hemoglobin mean values after 18 and 78 weeks of treatment, slight increases were observed in both empagliflozin treatment groups, whereas slight decreases were noted in the placebo group. At the 4-week follow-up values had started returning to baseline levels. Analyses of PCSAs revealed no differences between the treatment groups.

For the empagliflozin treatment groups, analyses of adjusted mean differences to placebo in absolute and percent change in lipid parameters from baseline to Week 18, and from baseline to Week 78, showed no major changes in lipid values.

Changes in mean uric acid values after 18 and 78 weeks of treatment were overall small in all treatment groups with a slight decrease noted for empagliflozin treatment and a slight increase noted for placebo treatment.

Overall in this study, pulse rate changes over time were only small and comparable in all treatment groups. Despite the observed reduction in blood pressure in the empagliflozin treatment groups, pulse rates did not increase.

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Conclusions:

In this 78-week study, treatment with empagliflozin 10 mg and 25 mg resulted in statistically significant and clinically meaningful reductions versus placebo in HbA_{1c} at Week 18 in patients receiving a stable background insulin dose. As insulin background dose could be adjusted after Week 18 to meet an FPG of <110 mg/dL, insulin sparing was achieved along with the reductions in HbA_{1c} at Week 78. These Week 78 results were accompanied by reductions in blood pressure, weight, and FPG. Discontinuations due to AEs and the incidence of urinary tract and genital infections were higher in the empagliflozin groups compared with the placebo group. However, the overall AE profile for both doses of empagliflozin treatment was generally similar to that of placebo and the incidence of hypoglycemic events was comparable across the 3 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 and results for secondary endpoints. 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
Basal insulin dose (IU) change from baseline at week 78 (Key Secondary endpoint)	Table 15.2.2.1.1: 1
HbA1c (%) change from baseline at week 78 (Key Secondary endpoint)	Table 15.2.2.2.1: 1
HbA1c <7% at week 18 (Secondary endpoint)	Table 15.2.3.1.1: 1
HbA1c <7% at week 78 (Secondary endpoint)	Table 15.2.3.1.1: 5
FPG (mg/dL) change from baseline at week 18 (Secondary endpoint) FPG (mg/dL) change from baseline at week 78 (Secondary endpoint)	Table 15.2.3.4: 1
Body weight (kg) change from baseline at week 18 (Secondary endpoint) Body weight (kg) change from baseline at week 78 (Secondary endpoint)	Table 15.2.3.5: 1

Table 15.1.1: 1 Disposition of patients at Week 18 - screened patients set

	Placebo N (%)	Empa 10mg N (%)	Empa 25mg N (%)	Total N (%)
Screened				826
Started placebo run-in				532
Not entered				332
Entered	170	169	155	494
Not treated	0	0	0	0
Treated	170 (100.0)	169 (100.0)	155 (100.0)	494 (100.0)
Not prematurely discontinued from trial medication	147 (86.5)	153 (90.5)	129 (83.2)	429 (86.8)
Prematurely discontinued from trial medication	23 (13.5)	16 (9.5)	26 (16.8)	65 (13.2)
Adverse event	8 (4.7)	6 (3.6)	13 (8.4)	27 (5.5)
Worsening of disease under study	0	0	0	0
Worsening of other pre-existing disease	0	2 (1.2)	0	2 (0.4)
Other adverse event	8 (4.7)	4 (2.4)	13 (8.4)	25 (5.1)
Lack of efficacy	1 (0.6)	0	0	1 (0.2)
Non compliant with protocol	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
Lost to follow-up	5 (2.9)	3 (1.8)	0	8 (1.6)
Patient refusal to continue, not due to AE	6 (3.5)	3 (1.8)	0	9 (1.8)
Other	2 (1.2)	3 (1.8)	12 (7.7)	17 (3.4)

'Entered' means randomised or assigned to open-label treatment.

Table 15.2.2.1.1: 1 Basal insulin dose change from baseline ANCOVA results at week 78 - FAS78-completers (LOCF-78)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	112	127	110
Number of analysed patients	112	127	110
Baseline mean (SE)	47.84 (3.11)	45.13 (2.62)	48.43 (2.79)
Week 78			
Values at visit			
Mean (SE)	52.63 (2.97)	44.43 (2.27)	48.04 (2.83)
Adjusted* mean (SE)	52.49 (1.58)	45.83 (1.48)	46.57 (1.59)
Change from baseline			
Mean (SE)	4.79 (2.06)	-0.70 (1.85)	-0.39 (1.06)
Adjusted* mean (SE)	5.45 (1.58)	-1.21 (1.48)	-0.47 (1.59)
Comparison vs Placebo			
Adjusted* mean (SE)		-6.66 (2.18)	-5.92 (2.25)
95.0% confidence interval		(-10.94,-2.38)	(-10.36,-1.49)
97.5% confidence interval		(-11.56,-1.77)	(-11.00,-0.85)
p-value		0.0024	0.0090

* Model for Week 78 includes baseline basal insulin (p<0.0001), baseline HbA1c (p=0.0133) as linear covariate(s) and geographical region (p=0.0002), treatment (p=0.0047) as fixed effect(s).

Table 15.2.2.2.1: 1 HbA1c (%) change from baseline ANCOVA results at week 78 - FAS78-completers (LOCF-78)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	112	127	110
Number of analysed patients	112	127	110
Baseline mean (SE)	8.09 (0.07)	8.27 (0.07)	8.29 (0.08)
Week 78			
Values at visit			
Mean (SE)	8.14 (0.11)	7.76 (0.08)	7.62 (0.09)
Adjusted* mean (SE)	8.20 (0.09)	7.74 (0.08)	7.58 (0.09)
Change from baseline			
Mean (SE)	0.05 (0.10)	-0.51 (0.09)	-0.68 (0.09)
Adjusted* mean (SE)	-0.02 (0.09)	-0.48 (0.08)	-0.64 (0.09)
Comparison vs Placebo			
Adjusted* mean (SE)		-0.46 (0.12)	-0.62 (0.12)
95.0% confidence interval		(-0.70,-0.23)	(-0.87,-0.38)
97.5% confidence interval		(-0.73,-0.19)	(-0.90,-0.34)
p-value		0.0001	<0.0001

* Model for Week 78 includes baseline HbA1c (p<0.0001) as linear covariate(s) and geographical region (p=0.6285), treatment (p<0.0001) as fixed effect(s).

Table 15.2.3.1.1: 1 Logistic regression for HbA1c <7% at week 18 - FAS (NCF)

	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	170	169	155
Number of analysed patients, N (%)	165 (100.0)	167 (100.0)	154 (100.0)
Number (%) satisfying HbA1c response <7.0% at week 18	9 (5.5)	30 (18.0)	30 (19.5)
95.0% Confidence interval [%]*	(2.5, 10.1)	(12.5, 24.6)	(13.5, 26.6)
Comparison vs Placebo			
Odds Ratio **		4.096	4.636
95.0% Confidence interval **		(1.846, 9.088)	(2.083, 10.321)
p-value **		0.0005	0.0002

* Exact 95% CI by Clopper and Pearson.
** Logistic regression includes treatment, geographical region and baseline HbA1c.

Source data: Appendix 16.2.6, Listing 1 s15\hbatbin2001.sas 12NOV2012

Table 15.2.3.1.1: 5 Logistic regression for HbA1c <7% at week 78 - FAS (NCF)

	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	170	169	155
Number of analysed patients, N (%)	165 (100.0)	167 (100.0)	154 (100.0)
Number (%) satisfying HbA1c response <7.0% at week 78	11 (6.7)	20 (12.0)	27 (17.5)
95.0% Confidence interval [%]*	(3.4, 11.6)	(7.5, 17.9)	(11.9, 24.5)
Comparison vs Placebo			
Odds Ratio **		1.939	3.239
95.0% Confidence interval **		(0.884, 4.256)	(1.518, 6.911)
p-value **		0.0986	0.0024

* Exact 95% CI by Clopper and Pearson.
** Logistic regression includes treatment, geographical region and baseline HbA1c.

Source data: Appendix 16.2.6, Listing 1 s15\hbatbin2001.sas 12NOV2012

Table 15.2.3.4: 1 FPG (mg/dL) change from baseline MMRM results over time - FAS (OC)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Week 12			
Values at visit			
Number of analysed patients	139	143	129
Mean (SE)	153.12 (4.24)	125.20 (3.28)	126.19 (2.85)
Adjusted* mean (SE)	154.12 (3.15)	126.30 (3.10)	123.72 (3.27)
Change from baseline			
Mean (SE)	10.88 (4.75)	-12.87 (3.81)	-19.60 (3.98)
Adjusted* mean (SE)	12.88 (3.15)	-14.94 (3.10)	-17.52 (3.27)
Comparison vs Placebo			
Adjusted* mean (SE)		-27.82 (4.42)	-30.39 (4.54)
95.0% confidence interval		(-36.50,-19.13)	(-39.31,-21.47)
p-value		<0.0001	<0.0001
Week 18			
Values at visit			
Number of analysed patients	135	138	120
Mean (SE)	151.50 (4.67)	123.49 (3.00)	121.48 (2.72)
Adjusted* mean (SE)	152.40 (3.30)	123.99 (3.26)	118.18 (3.49)
Change from baseline			
Mean (SE)	9.81 (5.48)	-14.79 (3.93)	-27.03 (3.92)
Adjusted* mean (SE)	11.15 (3.30)	-17.25 (3.26)	-23.06 (3.49)
Comparison vs Placebo			
Adjusted* mean (SE)		-28.40 (4.65)	-34.21 (4.81)
95.0% confidence interval		(-37.54,-19.27)	(-43.67,-24.76)
p-value		<0.0001	<0.0001

* Model includes, baseline fasting plasma glucose (p<0.0001) baseline HbA1c (p=0.0003) as linear covariate(s), geographical region (p<0.0001), treatment (p<0.0001), visit (p=0.0390) and visit by treatment interaction (p=0.0271) as fixed effect(s).

Source data: Appendix 16.2.6, Listing 2 s15\fpgtmmrm1001.sas 12NOV2012

Table 15.2.3.4: 1 FPG (mg/dL) change from baseline MMRM results over time - FAS (OC)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Week 78			
Values at visit			
Number of analysed patients	92	104	92
Mean (SE)	131.07 (4.15)	127.43 (3.44)	126.97 (4.08)
Adjusted* mean (SE)	135.76 (3.67)	130.73 (3.49)	123.81 (3.71)
Change from baseline			
Mean (SE)	-5.53 (4.95)	-7.75 (4.66)	-21.62 (5.13)
Adjusted* mean (SE)	-5.48 (3.67)	-10.51 (3.49)	-17.43 (3.71)
Comparison vs Placebo			
Adjusted* mean (SE)		-5.03 (5.07)	-11.95 (5.23)
95.0% confidence interval		(-15.01, 4.94)	(-22.24, -1.67)
p-value		0.3216	0.0229

* Model includes, baseline fasting plasma glucose (p<0.0001) baseline HbA1c (p=0.0003) as linear covariate(s), geographical region (p<0.0001), treatment (p<0.0001), visit (p=0.0390) and visit by treatment interaction (p=0.0271) as fixed effect(s).

Source data: Appendix 16.2.6, Listing 2 s15\fpgtmmrm1001.sas 12NOV2012

Table 15.2.3.5: 1 Body weight (kg) change from baseline MMRM results over time - FAS (OC)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Week 12			
Values at visit			
Number of analysed patients	145	152	133
Mean (SE)	91.28 (1.99)	90.92 (2.02)	92.43 (1.87)
Adjusted* mean (SE)	92.24 (0.78)	90.72 (0.76)	89.46 (0.82)
Change from baseline			
Mean (SE)	0.89 (0.84)	-0.60 (1.00)	-1.92 (0.16)
Adjusted* mean (SE)	0.86 (0.78)	-0.66 (0.76)	-1.91 (0.82)
Comparison vs Placebo			
Adjusted* mean (SE)		-1.52 (1.09)	-2.77 (1.13)
95.0% confidence interval		(-3.67, 0.62)	(-4.99,-0.55)
p-value		0.1640	0.0145
Week 18			
Values at visit			
Number of analysed patients	141	148	125
Mean (SE)	90.03 (1.91)	89.41 (1.62)	93.42 (2.49)
Adjusted* mean (SE)	91.32 (0.68)	89.28 (0.66)	90.45 (0.72)
Change from baseline			
Mean (SE)	-0.04 (0.21)	-2.06 (0.22)	-0.91 (1.27)
Adjusted* mean (SE)	-0.05 (0.68)	-2.09 (0.66)	-0.92 (0.72)
Comparison vs Placebo			
Adjusted* mean (SE)		-2.04 (0.95)	-0.87 (0.99)
95.0% confidence interval		(-3.90,-0.18)	(-2.81, 1.08)
p-value		0.0320	0.3818

* Model includes, baseline weight (p=0.6039) baseline HbA1c (p=0.1932) as linear covariate(s), geographical region (p=0.6095), treatment (p<0.0001), visit (p=0.0005) and visit by treatment interaction (p=0.0671) as fixed effect(s).

Source data: Appendix 16.2.6, Listing 3 s15\fpgtmmrm1001.sas 12NOV2012

Table 15.2.3.5: 1 Body weight (kg) change from baseline MMRM results over time - FAS (OC)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Week 78			
Values at visit			
Number of analysed patients	100	113	96
Mean (SE)	86.90 (2.54)	88.22 (1.85)	92.22 (2.17)
Adjusted* mean (SE)	92.54 (0.80)	88.91 (0.76)	89.42 (0.82)
Change from baseline			
Mean (SE)	1.12 (1.28)	-2.61 (0.31)	-1.99 (0.32)
Adjusted* mean (SE)	1.16 (0.80)	-2.47 (0.76)	-1.96 (0.82)
Comparison vs Placebo			
Adjusted* mean (SE)		-3.63 (1.10)	-3.12 (1.15)
95.0% confidence interval		(-5.81,-1.45)	(-5.39,-0.85)
p-value		0.0012	0.0073

* Model includes, baseline weight (p=0.6039) baseline HbA1c (p=0.1932) as linear covariate(s), geographical region (p=0.6095), treatment (p<0.0001), visit (p=0.0005) and visit by treatment interaction (p=0.0671) as fixed effect(s).

Source data: Appendix 16.2.6, Listing 3 s15\fpgtmmrm1001.sas 12NOV2012