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:		**EudraCT No.:** 2008-000641-54	
Name of active ingredient: BI 10773		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 21 SEP 2010	**Trial No. / U No.:** 1245.10 / U10-3573-02	**Date of trial:** 02 SEP 2008 - 31 OCT 2009	**Date of revision:** 01 November 2012

Title of trial:	A Phase II, randomized, parallel group safety, efficacy, and pharmacokinetics study of BI 10773 (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) administered orally once daily over 12 weeks compared double blind to placebo with an additional open-label sitagliptin arm in type 2 diabetic patients with insufficient glycemic control despite metformin therapy
Coordinating Investigator:	[redacted] MD
Trial sites:	Multicentre study, cf Appendix 16.1.4
Publication (reference):	Data of this study has not been published
Clinical phase:	IIb
Objectives:	The objective of the study was to investigate the efficacy, safety and pharmacokinetics of five doses of BI 10773 compared to placebo given for 12 weeks as add-on therapy to on-going metformin therapy in patients with Type 2 diabetes mellitus (T2DM) with insufficient glycemic control.
Methodology:	Randomized, double-blind, placebo controlled, parallel group comparison that included an open-label sitagliptin group.
No. of subjects:	
planned:	Enrolled: 896 Entered: 448

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actual:	Enrolled: 1031 Entered: 495

	Entered	Treated	Analyzed
BI 10773 1mg	71	71	71
BI 10773 5mg	71	71	71
BI 10773 10mg	71	71	71
BI 10773 25mg	70	70	70
BI 10773 50mg	70	70	70
Placebo	71	71	71
Sitagliptin open-label	71	71	71

Diagnosis and main criteria for inclusion:	Male and female patients with a diagnosis of T2DM and previously treated with metformin alone or with metformin and one other oral antidiabetic drug other than those described in the Exclusion Criteria (antidiabetic therapy has to be unchanged for at least 10 weeks prior to screening) Age ≥18 and <80 years, stable metformin therapy ≥1500 mg/day for at least 10 weeks, Body Mass Index (BMI) ≤40 kg/m^2 HbA1c (glycosylated hemoglobin A1c) at Visit 1A (Screening): for patients treated with metformin and one other oral antidiabetic drug: HbA1c ≥6.5% to ≤9.0%; for patients treated with metformin only: HbA1c >7.0% to ≤10.0% HbA1c at Visit 2 (start of Run-in) for all patients: HbA1c >7.0 to ≤10.0%
Test product:	BI 10773 1mg, 5 mg, and 25 mg tablet
dose:	1 mg, 5 mg, 10 mg, 25 mg, and 50 mg qd
mode of admin.:	Oral
batch no.:	B073000780, B073000791, B073000869
Reference therapy 1:	Placebo (matching BI 10773 tablets)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B073000702

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Reference therapy 2:	Sitagliptin (Januvia™) – open-label
dose:	100 mg qd
mode of admin.:	Oral
batch no.:	B083000705, B083000704, B093000299
Duration of treatment:	12 weeks
Criteria for evaluation:	
Efficacy:	HbA1c change from baseline and fasting plasma glucose (FPG) change from baseline
Safety:	Frequency and intensity of adverse events (AEs), laboratory evaluations, vital signs, ECG
Statistical methods:	The primary endpoint, change from baseline of HbA1c after 12 weeks of treatment, was analyzed in a linear model with the fixed effects as treatment group, number of previously used anti-diabetic medications, baseline HbA1c and random effect country. Similar methods were used to analyze the secondary endpoints as well as descriptive statistics. Descriptive statistics were used to evaluate the safety parameters. PK data are presented by using individual concentration-time data with descriptive statistics for trough concentrations.
SUMMARY – CONCLUSIONS:	
Efficacy results:	There were similar proportions of male (50.5 %) and female (49.5%) patients. The majority of patients were non-Hispanic white (84.6%, 419/495). Mean (SD) age was 58.3 (8.8) years with 25.1% of patients being 65 years or older. Mean (SD) BMI was 31.4 (4.5) kg/m^2 overall and mean (SD) weight was 89.0 (16.0) kg overall. Overall, 55.8 % of patients had diabetes for more than 5 years. At the time of enrollment, 63.2% of patients were taking metformin only and 36.8% were taking metformin plus one additional medication. The mean (SD) HbA1c among treatment groups ranged from 7.8% (0.7) to 8.1% (0.8) at baseline. Mean (SD) FPG level was in the range from 172.9 (40.4) mg/dL to 180.3 (43.2) mg/dL and mean (SD) FPI level ranged from 7.8 (4.2) µIU/mL to 10.4 (5.8) µIU/mL. The primary endpoint was HbA1c change from baseline at Week 12. All 5 doses of BI 10773 showed statistically significant placebo-corrected decrease in HbA1c, with largest decreases of 0.71 % in the BI 10773 10 mg dose group and

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	0.70% in the BI 10773 25 mg dose. Treatment with BI 10773 also showed a dose-dependent, placebo-corrected decrease in FPG at Week 12 ranging from 6.45 mg/dL to 32.66 mg/dL. These changes were statistically significant in all BI 10773 treatment groups, except the BI 10773 1 mg group. After 12 weeks of treatment with BI 10773, the mean body weight reduction ranged from 1.55 kg to 2.85 kg in the BI 10773 1 mg and 50 mg groups, respectively. The body weight was reduced by 1.16 kg in the placebo group. Weight decrease was statistically different from placebo for all groups, except for the BI 10773 1 mg group.. Additional analyses were performed for HbA1c over time and categorical responses of HbA1c. A repeated measure analysis demonstrated a statistically significant difference from placebo starting from week 4 for all groups except for the BI 10773 1 mg group. A logistic regression of the comparison of the proportion of patients with HbA1c $\leq$ 7% at week 12 showed a statistically significant difference for the BI 10773 10 mg (38.0%), 25 mg (37.1%) and 50 mg group (35.7%) compared to placebo (15.5%). Proportion of patients who had HbA1c reduction of at least 0.5% of at Week 12 ranged from 31% in the BI 10773 1 mg group to 60.6% and 60.0% in the BI 10773 10 mg and 25 mg groups, respectively, and it was statistically significantly different from placebo for all BI 10773 treatment groups in the logistic regression analysis.
Safety results:	Overall mean (SD) treatment duration was 83.2 (12.0) days. Mean treatment duration was comparable across the all treatment groups. Out of the 495 treated patients, 187 (37.8%) experienced at least 1 AE during treatment. Proportion of patients with AE ranged from 29.6% (21/71) to 48.6% (34/70) among the BI 10773 treatment groups and was 36.6% (26/71) in the placebo group and 35.2% (25/71) in the sitagliptin group. AEs most frequently reported among BI 10773 treatment groups include urinary tract infection (3.1%, 11/353), pollakiuria (2.5% 9/353), hypertension (2.0%, (7/353), and headache (2.0%, (7/353). The frequency of these events was similar to placebo and sitagliptin groups except for pollakiuria. Overall, the incidence of the adverse events varied among treatment groups without clear dose relationship. Adverse events of severe intensity were reported by only 3 patients, one patient in each of the BI 10773 5 mg (myocardial infarction), BI 10773 10 mg (blood pressure increased and nausea) and sitagliptin group (influenza).

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	AEs consistent with "Urinary tract infections", identified through a manual review, were reported by 5.7% (4/70) of patients in the BI 10773 25 mg group, 5.6% (4/71) in the BI 10773 10 mg group, 4.2% (3/70) in the BI 10773 50 mg group and by 2.8% (2/71) in all other groups including placebo and sitagliptin. AEs consistent with "Genital infections" were reported by 5.6% (4/71) of patients in the BI 10773 10 mg group, 4.2% (3/71) in the BI 10773 5 mg group, 1.4% (1/70) in the BI 10773 50 mg group, 1.4% (1/71) in the BI 10773 1 mg and sitagliptin groups, and none in the placebo and BI 10773 25 mg groups. A total of 9 patients (1.8%) discontinued study prematurely due to AE, including 2 patients in the BI 10773 1 mg group (2.8%), 4 patients in the BI 10773 10 mg group (5.6%) and 3 patients in the BI 10773 50 mg group (4.3%). Serious adverse events (SAEs) were reported by 2.2% (11/495) patients overall. These included 2 patients in the placebo group (2.8%), 3 patients in the BI 10773 5 mg group (4.2%), 1 patient in the BI 10773 10 mg group (1.4%), 2 patients in the BI 10773 25 mg group (2.9%) and 3 patients in the BI 10773 50 mg group (4.3%). The main reason for the events being SAE was hospitalization. There were no AE that were reported as an SAE more than once among the BI 10773 treatment groups. There were no deaths reported during the study. There did not appear to be any dose related change in laboratory results or a clear difference in proportion of patients with abnormal laboratory results in the BI 10773 treatment groups compared to placebo or sitagliptin. Changes in electrolytes were transient and there was no significant change in electrolytes from baseline to week 12. There appeared to be a dose-dependant decrease in systolic and diastolic blood pressure in the BI 10773 treatment groups with the greatest decrease in the BI 10773 25 mg dose group. Exploratory analysis indicated that statistically significant placebo-corrected systolic BP decrease was observed in the BI 10773 25 mg group (6.42 mmHg) and in the BI 10773 10 mg group (4.17 mmHg). Decreases in diastolic BP were not statistically significant.
Conclusions:	Based on the analysis of the primary endpoint and some of the important secondary endpoints, both 10 mg and 25 mg doses of BI 10773 were most efficacious in regard to HbA1c and FPG lowering. All doses of BI 10773 were well tolerated. These results confirm that inhibition of SGLT-2 by BI 10773 can lead to improved glucose metabolism with a good safety profile and warrant further development of BI 10773 for treatment of T2DM.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide complete disposition results and/or results of additional secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Change in HbA_{1c} from baseline at Week 12 (Primary endpoint)	Table 15.2.1.1: 2
Change in FPG (fasting plasma glucose) through 12 weeks (Secondary endpoint)	Table 15.2.2: 2
Change in body weight at week 12 (Secondary endpoint)	Table 15.2.9: 2
Change in HbA_{1c} over time (Secondary endpoint)	Table 15.2.3: 2
Patients with $HbA_{1c} \leq 7\%$ at 12 weeks (Secondary endpoint)	Table 15.2.4: 1
Patients with HbA_{1c} lowered $\leq 0.5\%$ at 12 weeks (Secondary endpoint)	Table 15.2.5: 1
Change in FPI (fasting plasma insulin) from baseline at week 12 (Secondary endpoint)	Table 15.2.6: 2
Change in HOMA−IR (Homeostasis Model Assessment for insulin resistance) from baseline to Week 12 (Secondary endpoint)	Table 15.2.7: 2
Change in HOMA−%B (Homeostasis Model Assessment for insulin sensitivity) from baseline to Week 12 (Secondary endpoint)	Table 15.2.8: 2

Table 15.1.1: 1 Disposition of subjects
Medication Termination

	Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50	Sitag
Enrolled							
Not entered/randomized							
Entered/randomized	71(100.0)	71(100.0)	71(100.0)	71(100.0)	70(100.0)	70(100.0)	71(100.0)
Not treated	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Treated	71(100.0)	71(100.0)	71(100.0)	71(100.0)	70(100.0)	70(100.0)	71(100.0)
Not prematurely discontinued from trial medication	66(93.0)	66(93.0)	70(98.6)	66(93.0)	70(100.0)	65(92.9)	70(98.6)
Prematurely discontinued from trial medication	5(7.0)	5(7.0)	1(1.4)	5(7.0)	0(0.0)	5(7.1)	1(1.4)
Adverse event	0(0.0)	2(2.8)	0(0.0)	4(5.6)	0(0.0)	3(4.3)	0(0.0)
AE study dis. worse	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AE other dis. worse	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AE other	0(0.0)	2(2.8)	0(0.0)	4(5.6)	0(0.0)	3(4.3)	0(0.0)
Lack of efficacy	3(4.2)	1(1.4)	1(1.4)	0(0.0)	0(0.0)	1(1.4)	0(0.0)
Non compl. protocol	0(0.0)	1(1.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.4)
Lost to follow-up	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Refused cont. medic.	2(2.8)	1(1.4)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	0(0.0)
Other	0(0.0)	0(0.0)	0(0.0)	1(1.4)	0(0.0)	0(0.0)	0(0.0)

Table 15.2.1.1: 2 Comparison of treatments for change of HbA1c from baseline at week 12 - FAS LOCF

	Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Number of patients	71	71	71	71	70	70
Mean HbA1c at baseline [%]	7.96	7.75	7.97	7.91	8.06	7.88
Change from Baseline						
Adjusted mean (SE)	0.15 (0.08)	-0.09 (0.08)	-0.23 (0.08)	-0.56 (0.08)	-0.55 (0.08)	-0.49 (0.08)
95% CI	(-0.00, 0.30)	(-0.24, 0.07)	(-0.39, -0.08)	(-0.71, -0.41)	(-0.70, -0.40)	(-0.64, -0.33)
HbA1c difference to Placebo [%]						
Adjusted mean (SE)		-0.24 (0.10)	-0.39 (0.10)	-0.71 (0.10)	-0.70 (0.10)	-0.64 (0.10)
95% CI		(-0.44, -0.03)	(-0.59, -0.18)	(-0.91, -0.51)	(-0.91, -0.50)	(-0.84, -0.43)
P-Value		0.0226	0.0002	<.0001	<.0001	<.0001

* Based on ANCOVA with terms for baseline, treatment, no. of previous anti-diabetic med, country (country as random, all other effects fixed)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1 efft2.sas 16FEB2010

Table 15.2.2: 2 Repeated measures analysis for change of FPG over time - FAS LOCF w/o Sitagliptin

			Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Number of patients			69	68	70	68	69	69
Mean FPG at baseline			174.13	172.85	180.30	173.41	180.04	174.99
Change from baseline at week 4	FPG[mg/dl]							
		Number of patients	69	68	70	68	69	69
		Adjusted mean (SE)	4.85 (3.42)	-4.10 (3.43)	-7.65 (3.39)	-23.76 (3.43)	-24.26 (3.41)	-23.05 (3.40)
		95% CI	(-1.88, 11.58)	(-10.84, 2.65)	(-14.32, -0.98)	(-30.50,-17.02)	(-30.96,-17.56)	(-29.74,-16.36)
		P-Value	0.1573	0.2330	0.0246	<.0001	<.0001	<.0001
	FPG difference to Placebo [mg/dl]							
		Adjusted mean (SE)		-8.95 (4.82)	-12.50 (4.78)	-28.61 (4.82)	-29.11 (4.80)	-27.90 (4.80)
		95% CI		(-18.42, 0.53)	(-21.90, -3.10)	(-38.08,-19.14)	(-38.55,-19.67)	(-37.33,-18.46)
		P-Value		0.0641	0.0093	<.0001	<.0001	<.0001

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 effrpt.sas 11DEC2009

Table 15.2.2: 2 Repeated measures analysis for change of FPG over time - FAS LOCF w/o Sitagliptin

			Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Change from baseline at week 8	FPG[mg/dl]							
		Number of patients	69	68	70	68	69	69
		Adjusted mean (SE)	2.50 (3.67)	-5.85 (3.68)	-10.57 (3.63)	-27.17 (3.68)	-27.05 (3.65)	-27.13 (3.65)
		95% CI	(-4.71, 9.71)	(-13.08, 1.38)	(-17.71, -3.43)	(-34.40,-19.94)	(-34.23,-19.86)	(-34.30,-19.96)
		P-Value	0.4951	0.1123	0.0038	<.0001	<.0001	<.0001
	FPG difference to Placebo [mg/dl]							
		Adjusted mean (SE)		-8.36 (5.17)	-13.07 (5.13)	-29.68 (5.17)	-29.55 (5.15)	-29.63 (5.15)
		95% CI		(-18.51, 1.80)	(-23.16, -2.99)	(-39.83,-19.52)	(-39.68,-19.43)	(-39.76,-19.51)
		P-Value		0.1067	0.0112	<.0001	<.0001	<.0001

Table 15.2.2: 2 Repeated measures analysis for change of FPG over time - FAS LOCF w/o Sitagliptin

			Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Change from baseline at week 12	FPG[mg/dl]							
		Number of patients	69	68	70	68	69	69
		Adjusted mean (SE)	4.75 (3.48)	-1.70 (3.49)	-15.84 (3.45)	-22.14 (3.49)	-26.83 (3.47)	-27.91 (3.46)
		95% CI	(-2.09, 11.59)	(-8.55, 5.16)	(-22.62, -9.06)	(-28.99,-15.28)	(-33.65,-20.02)	(-34.71,-21.10)
		P-Value	0.1729	0.6264	<.0001	<.0001	<.0001	<.0001
	FPG difference to Placebo [mg/dl]							
		Adjusted mean (SE)		-6.45 (4.90)	-20.59 (4.86)	-26.89 (4.90)	-31.58 (4.88)	-32.66 (4.88)
		95% CI		(-16.08, 3.18)	(-30.16,-11.03)	(-36.52,-17.26)	(-41.18,-21.98)	(-42.26,-23.06)
		P-Value		0.1887	<.0001	<.0001	<.0001	<.0001

Table 15.2.9: 2 Comparison of treatments for change of body weight at week 12 - FAS CLOCF

	Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50	Sitag
Number of patients	71	71	71	71	70	70	71
Mean weight at baseline [kg]	87.75	90.57	87.03	87.87	90.49	91.58	87.98
Change from Baseline							
Adjusted mean (SE)	-1.16 (0.31)	-1.55 (0.31)	-2.28 (0.31)	-2.74 (0.31)	-2.56 (0.31)	-2.85 (0.32)	-0.84 (0.31)
95% CI	(-1.78, -0.54)	(-2.17, -0.94)	(-2.90, -1.66)	(-3.36, -2.12)	(-3.18, -1.95)	(-3.47, -2.23)	(-1.46, -0.22)
weight difference to Placebo [kg]							
Adjusted mean (SE)		-0.40 (0.42)	-1.13 (0.42)	-1.58 (0.42)	-1.41 (0.42)	-1.69 (0.42)	0.31 (0.42)
95% CI		(-1.23, 0.43)	(-1.95, -0.30)	(-2.41, -0.76)	(-2.24, -0.58)	(-2.53, -0.86)	(-0.51, 1.14)
P-Value		0.3463	0.0079	0.0002	0.0010	<.0001	0.4558

* Based on ANCOVA with terms for baseline, treatment, no. of previous anti-diabetic med, country (country as random, all other effects fixed)

Source data: Appendix 16.1.9.2, Statdoc 6.9.4 efft2.sas 16FEB2010

Table 15.2.3: 2 Repeated measures analysis for change of HbA1c over time - FAS CLOCF

			Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Number of patients			71	71	71	71	70	70
Mean HbA1c at baseline			7.96	7.75	7.97	7.91	8.06	7.88
Change from baseline at week 4	HbA1c[%]							
		Number of patients	71	71	71	71	70	70
		Adjusted mean (SE)	0.03 (0.06)	-0.11 (0.06)	-0.15 (0.06)	-0.31 (0.06)	-0.30 (0.06)	-0.35 (0.06)
		95% CI	(-0.08, 0.14)	(-0.23, -0.00)	(-0.26, -0.04)	(-0.42, -0.20)	(-0.41, -0.19)	(-0.46, -0.24)
		P-Value	0.5911	0.0424	0.0094	<.0001	<.0001	<.0001
	HbA1c difference to Placebo [%]							
		Adjusted mean (SE)		-0.15 (0.08)	-0.18 (0.08)	-0.34 (0.08)	-0.33 (0.08)	-0.38 (0.08)
		95% CI		(-0.30, 0.00)	(-0.33, -0.03)	(-0.49, -0.19)	(-0.48, -0.18)	(-0.53, -0.23)
		P-Value		0.0580	0.0200	<.0001	<.0001	<.0001

Source data: Appendix 16.1.9.2, Statdoc 6.3.1 effrpt.sas 11DEC2009

Table 15.2.3: 2 Repeated measures analysis for change of HbA1c over time - FAS CLOCF

			Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Change from baseline at week 8	HbA1c[%]							
		Number of patients	71	71	71	71	70	70
		Adjusted mean (SE)	0.06 (0.07)	-0.14 (0.07)	-0.29 (0.07)	-0.56 (0.07)	-0.51 (0.07)	-0.52 (0.07)
		95% CI	(-0.08, 0.19)	(-0.27, -0.00)	(-0.43, -0.16)	(-0.69, -0.42)	(-0.64, -0.37)	(-0.66, -0.39)
		P-Value	0.4111	0.0430	<.0001	<.0001	<.0001	<.0001
	HbA1c difference to Placebo [%]							
		Adjusted mean (SE)		-0.19 (0.09)	-0.35 (0.09)	-0.61 (0.09)	-0.56 (0.09)	-0.58 (0.09)
		95% CI		(-0.38, -0.01)	(-0.53, -0.17)	(-0.80, -0.43)	(-0.75, -0.38)	(-0.76, -0.40)
		P-Value		0.0383	0.0002	<.0001	<.0001	<.0001

Table 15.2.3: 2 Repeated measures analysis for change of HbA1c over time - FAS CLOCF

			Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50
Change from baseline at week 12	HbA1c[%]							
		Number of patients	71	71	71	71	70	70
		Adjusted mean (SE)	0.13 (0.08)	-0.08 (0.08)	-0.26 (0.08)	-0.57 (0.08)	-0.58 (0.08)	-0.49 (0.08)
		95% CI	(-0.02, 0.28)	(-0.23, 0.07)	(-0.41, -0.11)	(-0.72, -0.42)	(-0.73, -0.43)	(-0.64, -0.34)
		P-Value	0.0841	0.3042	0.0008	<.0001	<.0001	<.0001
	HbA1c difference to Placebo [%]							
		Adjusted mean (SE)		-0.21 (0.11)	-0.39 (0.10)	-0.70 (0.10)	-0.71 (0.11)	-0.62 (0.11)
		95% CI		(-0.42, -0.00)	(-0.60, -0.18)	(-0.90, -0.49)	(-0.92, -0.50)	(-0.83, -0.42)
		P-Value		0.0464	0.0002	<.0001	<.0001	<.0001

Source data: Appendix 16.1.9.2, Statdoc 6.3.1 effrpt.sas 11DEC2009

Table 15.2.4: 1 Logistic regression of HbA1c categories at week 12
Proportion of patients with HbA1c less than equal to 7% - FAS CLOCF

Factor	Proportion of patients with HbA1c <= 7% at wk 12	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	Wald Chi-Sq	df	p-value
Placebo	11 / 71 (15.5)						
BI 1.0	17 / 71 (23.9)	1.52	0.58	3.99	0.73	1	0.3934
BI 5.0	15 / 71 (21.1)	1.99	0.75	5.28	1.90	1	0.1677
BI 10	27 / 71 (38.0)	5.13	2.01	13.12	11.65	1	0.0006
BI 25	26 / 70 (37.1)	6.51	2.51	16.89	14.81	1	0.0001
BI 50	25 / 70 (35.7)	4.33	1.67	11.21	9.12	1	0.0025
Sitag	24 / 71 (33.8)	4.72	1.80	12.38	9.96	1	0.0016

Covariates in the model: treatment, Baseline HbA1c, anti-diabetic medications
Odds ratios are with respect to placebo

Source data: Appendix 16.1.9.2, Statdoc 6.4.1

Table 15.2.5: 1 Logistic regression of HbA1c categories at week 12
Proportion of patients with HbA1c lowered at least 0.5% - FAS CLOCF

Factor	Proportion of patients with HbA1c lowered by at least 0.5% from baseline	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	Wald Chi-Sq	df	p-value
Placebo	15 / 71 (21.1)						
BI 1.0	22 / 71 (31.0)	2.39	1.05	5.44	4.31	1	0.0378
BI 5.0	29 / 71 (40.8)	3.18	1.43	7.05	8.10	1	0.0044
BI 10	43 / 71 (60.6)	8.42	3.74	18.94	26.51	1	<.0001
BI 25	42 / 70 (60.0)	7.22	3.21	16.23	22.87	1	<.0001
BI 50	34 / 70 (48.6)	5.10	2.29	11.37	15.86	1	<.0001
Sitag	38 / 71 (53.5)	5.24	2.34	11.73	16.26	1	<.0001

Covariates in the model: treatment, Baseline HbA1c, anti-diabetic medications
Odds ratios are with respect to placebo

Source data: Appendix 16.1.9.2, Statdoc 6.5.1

Table 15.2.6: 2 Comparison of treatments for change of FPI from baseline at week 12 - FAS CLOCF

	Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50	Sitag
Number of patients	63	59	60	59	57	61	59
Mean FPI at baseline	9.76	7.84	9.90	10.00	9.21	10.35	9.70
Change from Baseline							
Adjusted mean (SE)	0.43 (0.57)	0.09 (0.59)	-0.84 (0.58)	-1.77 (0.58)	-0.11 (0.59)	-1.52 (0.57)	1.84 (0.58)
95% CI	(-0.68, 1.55)	(-1.07, 1.24)	(-1.98, 0.30)	(-2.92, -0.63)	(-1.28, 1.06)	(-2.65, -0.38)	(0.69, 2.99)
FPI difference to Placebo							
Adjusted mean (SE)		-0.35 (0.79)	-1.27 (0.78)	-2.21 (0.79)	-0.55 (0.79)	-1.95 (0.78)	1.41 (0.79)
95% CI		(-1.90, 1.20)	(-2.81, 0.27)	(-3.75, -0.66)	(-2.10, 1.01)	(-3.48, -0.42)	(-0.14, 2.95)
P-Value		0.6583	0.1047	0.0052	0.4923	0.0126	0.0739

* Based on ANCOVA with terms for baseline, treatment, no. of previous anti-diabetic med, country (country as random, all other effects fixed)

Source data: Appendix 16.1.9.2, Statdoc 6.6.1 efft2.sas 16FEB2010

Table 15.2.7: 2 Comparison of treatments for change of HOMA - IR from baseline at week 12 - FAS CLOCF

	Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50	Sitag
Number of patients	62	58	59	59	57	59	59
Mean HOMA-IR at baseline	4.24	3.36	4.24	4.31	3.92	4.46	4.24
Change from Baseline							
Adjusted mean (SE)	0.23 (0.26)	-0.11 (0.27)	-0.60 (0.26)	-1.04 (0.26)	-0.52 (0.27)	-1.10 (0.27)	0.48 (0.26)
95% CI	(-0.28, 0.74)	(-0.64, 0.41)	(-1.12, -0.08)	(-1.56, -0.52)	(-1.05, 0.00)	(-1.62, -0.57)	(-0.04, 1.00)
HOMA-IR difference to Placebo							
Adjusted mean (SE)		-0.35 (0.36)	-0.83 (0.36)	-1.27 (0.36)	-0.76 (0.36)	-1.33 (0.36)	0.25 (0.36)
95% CI		(-1.06, 0.37)	(-1.54, -0.12)	(-1.98, -0.56)	(-1.47, -0.04)	(-2.04, -0.62)	(-0.46, 0.96)
P-Value		0.3402	0.0221	0.0005	0.0384	0.0003	0.4893

* Based on ANCOVA with terms for baseline, treatment, no. of previous anti-diabetic med, country (country as random, all other effects fixed)

Source data: Appendix 16.1.9.2, Statdoc 6.7.1 efft2.sas 16FEB2010

Table 15.2.8: 2 Comparison of treatments for change of HOMA - %B from baseline at week 12 - FAS CLOCF

	Placebo	BI 1.0	BI 5.0	BI 10	BI 25	BI 50	Sitag
Number of patients	62	58	58	59	57	59	59
Mean HOMA-%B at baseline	36.96	29.55	36.62	35.55	34.97	37.28	34.28
Change from Baseline							
Adjusted mean (SE)	0.30 (2.70)	0.08 (2.77)	0.36 (2.76)	1.55 (2.72)	6.68 (2.78)	4.01 (2.76)	12.38 (2.75)
95% CI	(-5.04, 5.64)	(-5.40, 5.56)	(-5.10, 5.82)	(-3.84, 6.93)	(1.18, 12.18)	(-1.47, 9.48)	(6.95, 17.81)
HOMA-%B difference to Placebo							
Adjusted mean (SE)		-0.22 (3.72)	0.06 (3.72)	1.25 (3.70)	6.38 (3.73)	3.71 (3.69)	12.08 (3.70)
95% CI		(-7.53, 7.10)	(-7.25, 7.38)	(-6.03, 8.52)	(-0.96, 13.72)	(-3.55, 10.97)	(4.82, 19.35)
P-Value		0.9534	0.9863	0.7359	0.0881	0.3154	0.0012

* Based on ANCOVA with terms for baseline, treatment, no. of previous anti-diabetic med, country (country as random, all other effects fixed)

Source data: Appendix 16.1.9.2, Statdoc 6.8.1 efft2.sas 16FEB2010