Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.:** 2008-000640-14	
Name of active ingredient: BI 10773		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 SEP 2010	**Trial No. / U No.:** 1245.9 / U10-2261-04	**Dates of trial:** 15 OCT 2008 – 1 OCT 2009	**Date of revision:** 15 OCT 2012

Title of trial:	A Phase IIb, randomized, parallel group safety, efficacy, and pharmacokinetics study of BI 10773 (5 mg, 10 mg and 25 mg) administered orally once daily over 12 weeks compared double blind to placebo, as monotherapy, with an additional open-label metformin arm in type 2 diabetic patients with insufficient glycemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multicenter study; 75 sites in 13 countries
Publication (reference):	Data of this study have not been published
Clinical phase:	IIb
Objectives:	Evaluation of safety, efficacy and pharmacokinetics of 3 different doses of BI 10773
Methodology:	Randomised double-blind, placebo controlled, parallel group comparison. The study also included an open-label metformin arm. Primary comparison was the change from baseline of glycosilated haemoglobin A1c (HbA1c) after 12 weeks of treatment in a linear model including the fixed effects treatment group, number of previously used anti-diabetic medications, baseline HbA1c and the random effect country. Patients were randomised to either one of the 3 doses of BI 10773 or placebo or metformin. The randomisation was performed via an IVRS system and was stratified by country and by number of previous anti-diabetic medications. For patients who were treatment-naïve no wash-out was required. For patients who were pretreated with a maximum of 1 oral antidiabetic medication, a 4 week wash-out from antidiabetic treatment was required in addition to the 2 weeks placebo run-in period. All patients had 2 weeks of placebo run-in, and 12 weeks of treatment. During the trial, the trial independent Data Monitoring Committee (DMC) monitored results and had to decide whether the allocation ratio was to be changed and whether any active dose groups of BI 10773 were to be stopped. The placebo and open-label metformin arms were not to be stopped during the trial.

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No. of subjects:

planned: entered: 320 patients

actual: enrolled: 848 patients

entered: 408 patients

	entered	treated	analysed (for primary endpoint)
BI 10773 5mg	81	81	81
BI 10773 10mg	81	81	81
BI 10773 25mg	82	82	82
Placebo	82	82	82
Metformin open-label	82	80	80

Diagnosis and main criteria for inclusion: Male and female patients, age ≥18 and <80 years, with a diagnosis of type 2 diabetes mellitus, either treatment-naïve (on no antidiabetic therapy for the 10 weeks prior to screening) or on a maximum of 1 oral antidiabetic therapy (except glitazones, glucagons-like peptide 1 analogues or insulin) on a stable dose for the 10 weeks prior to screening; HbA1c at screening for patients treated with 1 other oral antidiabetic drug: HbA1c ≥6.5 to ≤9.0% and for treatment-naïve patients: HbA1c >7.0 to ≤10.0%; HbA1c at Visit 2 (start of run-in) for all patients: HbA1c >7.0 to ≤10.0%; body mass index (BMI) ≤40 kg/m^2

Test product: BI 10773

dose: 5 mg, 10 mg, or 25 mg
(10 mg dose given as two 5 mg BI 10773 tablets; 5 mg and 25 mg doses given as one BI 10773 tablet and one placebo tablet to maintain blinding; both 5 mg and 25 mg tablets were identical in appearance)

mode of admin.: Tablets per os, once daily

batch no.: B073000791 (5 mg), B073000869 (25 mg)

Reference therapy: Placebo, matching the BI 10773 tablets in appearance

dose: Not applicable

mode of admin.: Tablets per os, once daily

batch no.: B073000702

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Reference therapy:	Metformin - open-label
dose:	500 mg bid for 4 weeks, then 1000 mg bid or up to the maximum tolerated dose for 8 weeks
mode of admin.:	Immediate release tablets per os, twice daily
batch no.:	B083000771
Duration of treatment:	12 weeks
Criteria for evaluation:	
Efficacy:	The primary endpoint in this study was the HbA1c change from baseline after 12 weeks of treatment Secondary efficacy endpoints included the fasting plasma glucose (FPG) change from baseline after 12 weeks of treatment, the change of HbA1c and FPG over time, the proportions of patients achieving an HbA1c $\leq$7.0% or an HbA1c lowering of at least 0.5% after 12 weeks of treatment, and the changes in fasting plasma insulin, HOMA index and body weight after 12 weeks of treatment. In addition the pharmacokinetics of BI 10773 was investigated.
Safety:	Frequency and intensity of adverse events (AEs), laboratory evaluation, vital signs (pulse rate, blood pressure) and 12-lead ECG
Statistical methods:	The efficacy endpoints were analysed with an ANCOVA model including the fixed effects treatment group, number of previously used anti-diabetic medications, baseline HbA1c, and country as random effect. Pharmacokinetic data was analysed using descriptive statistics for trough concentrations. Descriptive statistics were used for the evaluation of safety parameters.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Demographic baseline characteristics were comparable between treatment groups. Overall, 52.0% of patients were male, 63.8% of patients were white and 34.5% were Asian. The overall mean age was 57.5 years (standard deviation [SD]: 9.8) and the mean BMI was 29.0 kg/m^2 (SD: 4.6). In total 40.6% of patients had been pre-treated with 1 antidiabetic drug and therefore completed a4-week wash-out period before randomisation. At the time of enrolment, 31.0% of patients had diabetes for more than 5 years. The mean HbA1c per treatment group ranged from 7.8% to 8.1% at baseline.

The primary endpoint of this study was the mean change from baseline in HbA1c after 12 weeks of treatment. This was analysed using an ANCOVA with treatment as a fixed effect, baseline HbA1c, and number of previous anti-diabetic medications, and country as a random effect, using a modified LOCF approach. The mean HbA1c decreased from baseline in all dose groups. For all 3 blinded BI 10773 treatment groups, the reduction was statistically significant and clinically meaningful, compared with placebo (5 mg: -0.52%, 10 mg: -0.57%, 25 mg: -0.72%). The open-label arm of metformin had been included in the trial as a sensitivity measure. Accordingly, the efficacy results of metformin were not compared with the efficacy results of BI 10773. The reported mean final dose of metformin after 12 weeks of treatment was 1668.8 mg. Mean adjusted HbA1c at week 12 for the open-label arm was reduced by -0.82%.

Sensitivity analyses on the primary endpoint and the analyses of the secondary endpoints (change from baseline in FPG, FPI, HOMA indeces, and categorical HbA1c response) supported the results of the primary analysis. For change from baseline of FPG at week 12, all BI 10773 treatment groups had a reduction in FPG, compared with placebo (5 mg: -24.05 mg/dL, 10 mg: -29.71 mg/dL, 25 mg: -31.88 mg/dL). After 12 weeks of treatment with BI 10773, the adjusted mean body weight was reduced in all treatment groups (5 mg BI 10773: -1.06 kg, 10 mg: -1.58 kg, 25 mg: -1.28 kg, open-label metformin: -0.58 kg), compared with placebo.

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Safety results:

Out of 406 treated patients, 129 patients (31.8%) experienced at least 1 AE during the randomised treatment period. The incidence of AEs was comparable between treatment groups (32.9% for patients in the placebo group, 38.8% for patients in the metformin group, and 29.1% for patients in the 3 combined BI 10773 treatment groups). There was no dose-dependent increase in the incidence of AEs in the BI 10773 treatment groups.

The most frequently reported AEs on MedDRA preferred term level were diarrhoea (9 patients, 2.2% in total; of those 7 patients in the open-label metformin group), pollakiuria, thirst (8 patients each, 2.0%; only reported for patients in the BI 10773 treatment groups), and nasopharyngitis (7 patients, 1.7%; similar incidence across all 5 treatment groups). Most AEs reported in this trial were of mild or moderate intensity. A total of 7 patients reported AEs of severe intensity: 3 in the 5 mg BI 10773 group and 4 in the metformin group.

Overall, 6 patients discontinued treatment prematurely due to AEs. Three of these patients were in the BI 10773 treatment groups (2 patients receiving 5 mg and 1 patient receiving 25 mg) and 3 in the metformin group; no patient in the placebo group discontinued due to an AE. Adverse events assessed by investigators as related to trial medication were reported in 26 patients in total: 2 (2.4%) in the placebo group, 10 (12.5%) in the metformin group, and 14 (5.7%) in the BI 10773 treatment groups (5 mg: 3 patients, 10 mg: 6 patients, 25 mg: 5 patients). The most frequently reported related AEs were thirst (7 patients in total, all in the 3 BI 10773 treatment groups), pollakiuria (6 patients in total, all in the 3 BI 10773 treatment groups), and diarrhoea (5 patients in total, all in the metformin group).

During the randomised treatment period, 6 patients experienced at least 1 serious adverse event (SAE): 2 patients in the 5 mg BI 10773 dose group, 1 patient in the 25 mg BI 10773 dose group, and 3 patients in the open-label metformin group. All of the SAEs had required hospitalisation and therapy. All but 2 SAEs led to premature discontinuation of trial medication. None of the SAEs was assessed as drug related by the investigator. All patients with SAEs had recovered or were sufficiently followed up until the end of the trial. No patient died during randomised treatment, 1 patient died during the wash-out period before randomisation. During the screening, wash-out and run-in periods, SAEs were reported for 4 patients that were subsequently not randomised.

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Safety results (continued):	The evaluation of clinical laboratory parameters generally showed low incidences of transitions relative to the reference ranges and of possibly clinically significant abnormalities. In all BI 10773 treatment groups, haematocrit and haemoglobin increased in a dose-dependent manner from baseline to the end of the treatment period. However, there were no patients with possibly clinically significant increases of these haematology parameters. For electrolytes and enzymes, some changes in mean values and shifts relative to reference ranges were observed, but these changes showed no apparent pattern of a systematic impact of any treatment arm. Concerning vital signs (blood pressure, pulse rate) and ECGs, there were no safety issues for any of the treatment groups.
Conclusions:	This study demonstrated that all administered doses of BI 10773 (5 mg, 10 mg, and 25 mg) were superior to placebo in terms of reduction of mean adjusted HbA1c levels, FPG levels, and body weight after 12 weeks of treatment. The mean differences to placebo in HbA1c were -0.52% for 5 mg, -0.57% for 10 mg, and -0.72% for 25 mg BI 10773. The effect on change from baseline for both HbA1c and FPG increased with the BI 10773 dose, indicating a dose-response relationship. Overall, all doses of BI 10773 were well tolerated and the analysis of adverse events and clinical laboratory parameters demonstrated a good safety profile of BI 10773 in patients with type 2 diabetes mellitus.

Trial Synopsis – Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the patient disposition results and the results for the primary and secondary endpoints 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**
Patient Disposition	Table 15.1.1: 1
Change of HbA1c from baseline at week 12 (Primary Endpoint)	Table 15.2.1.1: 4*
Change in FPG from baseline through 12 weeks of treatment (Secondary Endpoint)	Table 15.2.2: 5
Change from baseline of body weight after 12 weeks of treatment (Secondary Endpoint)	Table 15.2.9: 2
Change of HbA1c from baseline over time (Secondary Endpoint)	Table 15.2.3: 4
Patients with HbA1c ≤7.0% after 12 weeks of treatment (Secondary Endpoint)	Table 15.2.4: 1
Patients with an HbA1c lowering of at least 0.5% after 12 weeks of treatment (Secondary Endpoint)	Table 15.2.5: 1
Change from baseline of fasting plasma insulin (FPI) through 12 weeks of treatment (Secondary Endpoint)	Table 15.2.6: 2
Change from baseline in HOMA index for insulin resistance after 12 weeks of treatment (Secondary Endpoint)	Table 15.2.7: 2
Change from baseline in HOMA index for beta cell function after 12 weeks of treatment (Secondary Endpoint)	Table 15.2.8: 2
Dose normalized trough concentrations at Day 28, 56 and 84 (Secondary Endpoint)	Table 15.6.3: 2

* There is a minor difference between the data reported for the open label arm in the synopsis for this endpoint and that reported in the appended table due to the use of two analysis models.

Table 15.1.1: 1 Disposition of subjects
Medication Termination

	Placebo	BI 5.0	BI 10	BI 25	Metf	Total
Enrolled						848
Not entered/randomized						440
Entered/randomized	82(100.0)	81(100.0)	81(100.0)	82(100.0)	82(102.5)	408(100.5)
Not treated	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(2.5)	2(0.5)
Treated	82(100.0)	81(100.0)	81(100.0)	82(100.0)	80(100.0)	406(100.0)
Not prematurely discontinued from trial medication	76(92.7)	74(91.4)	80(98.8)	81(98.8)	74(92.5)	385(94.8)
Prematurely discontinued from trial medication	6(7.3)	7(8.6)	1(1.2)	1(1.2)	6(7.5)	21(5.2)
Adverse event	0(0.0)	2(2.5)	0(0.0)	1(1.2)	3(3.8)	6(1.5)
AE study dis. worse	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)	1(1.2)	0(0.0)	0(0.0)	1(1.3)	2(0.5)
AE other	0(0.0)	1(1.2)	0(0.0)	1(1.2)	2(2.5)	4(1.0)
Lack of efficacy	3(3.7)	0(0.0)	0(0.0)	0(0.0)	2(2.5)	5(1.2)
Non compl. protocol	1(1.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.2)
Lost to follow-up	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Refused cont. medic.	0(0.0)	2(2.5)	0(0.0)	0(0.0)	0(0.0)	2(0.5)
Other	2(2.4)	3(3.7)	1(1.2)	0(0.0)	1(1.3)	7(1.7)

Table 15.2.1.1: 4 Comparison of treatments for change of HbA1c from baseline at week 12 - FAS LOCF with all treatments

	Placebo	BI 5.0	BI 10	BI 25	Metf
Number of patients	82	81	81	82	80
Mean HbA1c at baseline [%]	7.81	7.93	7.99	7.81	8.14
Change from Baseline					
Adjusted mean (SE)	0.07 (0.08)	-0.45 (0.08)	-0.50 (0.08)	-0.65 (0.08)	-0.73 (0.08)
95% CI	(-0.09, 0.23)	(-0.61, -0.29)	(-0.66, -0.34)	(-0.81, -0.49)	(-0.89, -0.57)
HbA1c difference to Placebo [%]					
Adjusted mean (SE)		-0.52 (0.11)	-0.57 (0.11)	-0.72 (0.11)	-0.80 (0.11)
95% CI		(-0.73, -0.30)	(-0.79, -0.36)	(-0.93, -0.51)	(-1.01, -0.58)
P-Value		<.0001	<.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 6.1.2.20 efft2.sas 04FEB2010

Table 15.2.2: 5 Repeated measures analysis for change of FPG over time - FAS LOCF with all treatments

			Placebo	BI 5.0	BI 10	BI 25	Metf
Change from baseline at week 12	FPG[mg/dl]						
		Number of patients	82	80	80	82	80
		Adjusted mean (SE)	0.41 (3.39)	-23.97 (3.44)	-29.51 (3.43)	-31.48 (3.39)	-29.36 (3.43)
		95% CI	(-6.31, 7.13)	(-30.77,-17.16)	(-36.31,-22.72)	(-38.19,-24.77)	(-36.16,-22.57)
		P-Value	0.9040	<.0001	<.0001	<.0001	<.0001
	FPG difference to Placebo [mg/dl]						
		Adjusted mean (SE)		-24.38 (4.33)	-29.92 (4.33)	-31.89 (4.29)	-29.77 (4.32)
		95% CI		(-32.88,-15.87)	(-38.43,-21.42)	(-40.33,-23.45)	(-38.27,-21.28)
		P-Value		<.0001	<.0001	<.0001	<.0001

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

	Placebo	BI 5.0	BI 10	BI 25	Metf
Number of patients	82	81	81	82	80
Mean weight at baseline [kg]	83.37	81.47	78.46	82.18	81.70
Change from Baseline					
Adjusted mean (SE)	-0.75 (0.26)	-1.81 (0.26)	-2.33 (0.26)	-2.03 (0.26)	-1.32 (0.26)
95% CI	(-1.26, -0.23)	(-2.32, -1.29)	(-2.84, -1.82)	(-2.54, -1.52)	(-1.84, -0.81)
weight difference to Placebo [kg]					
Adjusted mean (SE)		-1.06 (0.32)	-1.58 (0.32)	-1.28 (0.32)	-0.58 (0.32)
95% CI		(-1.68, -0.44)	(-2.21, -0.96)	(-1.90, -0.66)	(-1.20, 0.05)
P-Value		0.0009	<.0001	<.0001	0.0699

* 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 04FEB2010

Table 15.2.3: 4 Repeated measures analysis for change of HbA1c over time - FAS CLOCF with all treatments

			Placebo	BI 5.0	BI 10	BI 25	Metf
Number of patients			82	81	81	82	80
Mean HbA1c at baseline			7.81	7.93	7.99	7.81	8.14
Change from baseline at week 4	HbA1c[%]						
		Number of patients	82	81	81	82	80
		Adjusted mean (SE)	-0.01 (0.06)	-0.27 (0.06)	-0.24 (0.06)	-0.39 (0.06)	-0.26 (0.07)
		95% CI	(-0.14, 0.12)	(-0.40, -0.14)	(-0.37, -0.11)	(-0.52, -0.26)	(-0.39, -0.13)
		P-Value	0.8729	0.0001	0.0004	<.0001	0.0002
	HbA1c difference to Placebo [%]						
		Adjusted mean (SE)		-0.26 (0.08)	-0.23 (0.08)	-0.38 (0.08)	-0.25 (0.08)
		95% CI		(-0.42, -0.09)	(-0.39, -0.07)	(-0.54, -0.22)	(-0.41, -0.09)
		P-Value		0.0020	0.0054	<.0001	0.0025

Source data: Appendix 16.1.9.2, Statdoc 6.3.3 effrpt.sas 04FEB2010

Table 15.2.3: 4 Repeated measures analysis for change of HbA1c over time - FAS CLOCF with all treatments

			Placebo	BI 5.0	BI 10	BI 25	Metf
Change from baseline at week 8	HbA1c[%]						
		Number of patients	82	81	81	82	80
		Adjusted mean (SE)	0.04 (0.07)	-0.43 (0.08)	-0.53 (0.08)	-0.58 (0.07)	-0.59 (0.08)
		95% CI	(-0.11, 0.19)	(-0.58, -0.28)	(-0.68, -0.38)	(-0.73, -0.43)	(-0.74, -0.44)
		P-Value	0.6201	<.0001	<.0001	<.0001	<.0001
	HbA1c difference to Placebo [%]						
		Adjusted mean (SE)		-0.47 (0.10)	-0.56 (0.10)	-0.62 (0.10)	-0.63 (0.10)
		95% CI		(-0.66, -0.28)	(-0.76, -0.37)	(-0.81, -0.43)	(-0.82, -0.43)
		P-Value		<.0001	<.0001	<.0001	<.0001

Table 15.2.3: 4 Repeated measures analysis for change of HbA1c over time - FAS CLOCF with all treatments

			Placebo	BI 5.0	BI 10	BI 25	Metf
Change from baseline at week 12	HbA1c[%]						
		Number of patients	82	81	81	82	80
		Adjusted mean (SE)	0.07 (0.08)	-0.47 (0.08)	-0.53 (0.08)	-0.66 (0.08)	-0.78 (0.08)
		95% CI	(-0.09, 0.24)	(-0.64, -0.31)	(-0.70, -0.37)	(-0.82, -0.49)	(-0.95, -0.61)
		P-Value	0.3951	<.0001	<.0001	<.0001	<.0001
	HbA1c difference to Placebo [%]						
		Adjusted mean (SE)		-0.54 (0.11)	-0.60 (0.11)	-0.73 (0.11)	-0.85 (0.11)
		95% CI		(-0.76, -0.32)	(-0.82, -0.38)	(-0.95, -0.51)	(-1.07, -0.63)
		P-Value		<.0001	<.0001	<.0001	<.0001

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	18 / 82 (22.0)						
BI 5.0	27 / 81 (33.3)	2.60	1.12	6.03	4.96	1	0.0260
BI 10	24 / 81 (29.6)	2.60	1.12	6.03	4.94	1	0.0262
BI 25	37 / 82 (45.1)	4.14	1.83	9.35	11.68	1	0.0006
Metf	36 / 80 (45.0)	8.02	3.33	19.31	21.57	1	<.0001

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

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	21 / 82 (25.6)						
BI 5.0	38 / 81 (46.9)	2.74	1.31	5.75	7.18	1	0.0074
BI 10	48 / 81 (59.3)	4.89	2.29	10.47	16.72	1	<.0001
BI 25	49 / 82 (59.8)	5.88	2.76	12.51	21.10	1	<.0001
Metf	57 / 80 (71.3)	8.32	3.81	18.15	28.35	1	<.0001

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

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

	Placebo	BI 5.0	BI 10	BI 25	Metf
Number of patients	70	69	70	77	68
Mean FPI at baseline	10.54	8.66	8.41	8.86	8.86
Change from Baseline					
Adjusted mean (SE)	-0.95 (0.53)	-0.90 (0.53)	-1.02 (0.53)	-0.90 (0.50)	-0.01 (0.54)
95% CI	(-1.99, 0.09)	(-1.95, 0.15)	(-2.06, 0.02)	(-1.89, 0.09)	(-1.07, 1.04)
FPI difference to Placebo					
Adjusted mean (SE)		0.05 (0.75)	-0.07 (0.75)	0.05 (0.73)	0.94 (0.75)
95% CI		(-1.43, 1.53)	(-1.54, 1.40)	(-1.38, 1.49)	(-0.54, 2.42)
P-Value		0.9461	0.9234	0.9431	0.2126

* 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 04FEB2010

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

	Placebo	BI 5.0	BI 10	BI 25	Metf
Number of patients	70	69	70	77	68
Mean HOMA-IR at baseline	4.52	3.83	3.72	3.79	3.92
Change from Baseline					
Adjusted mean (SE)	-0.19 (0.26)	-0.85 (0.27)	-0.83 (0.26)	-0.79 (0.25)	-0.37 (0.27)
95% CI	(-0.72, 0.33)	(-1.38, -0.32)	(-1.36, -0.31)	(-1.28, -0.29)	(-0.90, 0.16)
HOMA-IR difference to Placebo					
Adjusted mean (SE)		-0.66 (0.36)	-0.64 (0.36)	-0.59 (0.35)	-0.18 (0.36)
95% CI		(-1.36, 0.04)	(-1.34, 0.06)	(-1.28, 0.09)	(-0.88, 0.53)
P-Value		0.0660	0.0736	0.0906	0.6180

* 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 04FEB2010

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

	Placebo	BI 5.0	BI 10	BI 25	Metf
Number of patients	70	69	70	77	68
Mean HOMA-%B at baseline	38.24	31.04	30.69	33.42	30.41
Change from Baseline					
Adjusted mean (SE)	-5.20 (2.56)	4.22 (2.57)	1.09 (2.54)	2.13 (2.43)	6.69 (2.58)
95% CI	(-10.29, -0.11)	(-0.90, 9.34)	(-3.97, 6.15)	(-2.72, 6.97)	(1.56, 11.83)
HOMA-%B difference to Placebo					
Adjusted mean (SE)		9.42 (3.25)	6.29 (3.24)	7.33 (3.15)	11.89 (3.26)
95% CI		(3.03, 15.81)	(-0.08, 12.65)	(1.12, 13.53)	(5.48, 18.30)
P-Value		0.0040	0.0528	0.0208	0.0003

* 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 04FEB2010

Table 15.6.3: 2 Comparison of pharmacokinetic parameters (N, Mean and CV [%]) of BI 10773 by treatment

	5 mg			10 mg			25 mg		
	N	Mean	CV [%]	N	Mean	CV [%]	N	Mean	CV [%]
$C_{pre,1}$ [nmol/L]	---	---	---	---	---	---	---	---	---
$C_{pre,28}$ [nmol/L]	67	31.6	158	75	61.7	169	77	117	154
$C_{pre,56}$ [nmol/L]	69	20.3	128	73	51.6	190	75	127	140
$C_{pre,84}$ [nmol/L]	70	22.9	132	77	55.3	156	75	118	179