Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**		Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2005-004597-24		
Name of active ingredient: BI 1356		**Page:** 1 of 5	**Number:**	**Synopsis No.:**
Ref. to Documentation:	**Module:**	**Volume:**		
Report date: 23 JAN 2008	**Trial No. / U No.:** 1218.6 / U08-1056-03	**Date of trial:** 28 APR 2006 – 21 AUG 2007		**Date of revision:** 22 OCT 2009

Title of trial:	A randomised, double-blind, placebo-controlled, five parallel groups study investigating the efficacy and safety of BI 1356 (1 mg, 5 mg and 10 mg administered orally once daily) over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycaemic control despite metformin therapy, including an open-label glimepiride treatment arm
Coordinating Investigator:	[redacted] Germany
Trial sites:	Multi-centre study, 47 centres in 6 countries (France, Germany, Slovakia, Sweden, Ukraine, and United Kingdom)
Publication (reference):	Data of this study has not been published
Clinical phase:	II b
Objectives:	To investigate the efficacy, safety, and tolerability of BI 1356 versus placebo, to explore the efficacy of glimepiride treatment vs. placebo for sensitivity analysis and to investigate population pharmacokinetics
Methodology:	Randomised, double-blind, placebo-controlled, open-label glimepiride, parallel group comparison
No. of subjects:	
planned:	entered: 375
actual:	enrolled: 669
	Treatment: Placebo entered: 71 treated: 71 analysed (for primary endpoint): 70 Treatment: 1 mg of BI 1356 entered: 65 treated: 65 analysed (for primary endpoint): 64 Treatment: 5 mg of BI 1356 entered: 66 treated: 66 analysed (for primary endpoint): 62 Treatment: 10 mg of BI 1356 entered: 66 treated: 66 analysed (for primary endpoint): 66 Treatment: Glimepiride entered: 65 treated: 65 analysed (for primary endpoint): 64

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Diagnosis and main criteria for inclusion:	Patients ≥21 and ≤75 years with type 2 diabetes with insufficient glycaemic control despite metformin
Test product:	BI 1356 as an add-on therapy to metformin
dose:	1 mg, 5 mg, or 10 mg once daily
mode of admin.:	Tablets per os
batch no.:	B051001011 (1 mg), B051001015 (5 mg), B051000968 (10 mg)
Reference therapy:	Placebo as an add-on therapy to metformin
dose:	Matching for test product for each dose group, once daily
mode of admin.:	Tablets per os
batch no.:	B051000964 (for 1 mg), B051001178 (for 5 mg), B051001191 (for 10 mg)
Reference therapy:	Glimepiride as an add-on therapy to metformin
dose:	1 mg up to 3 mg, once daily
mode of admin.:	Tablets per os
batch no.:	B051001531 (1 mg), B051001532 (2 mg), B051001533 (3 mg)
Duration of treatment:	For patients pre-treated with metformin and one additional oral antidiabetic agent: 6 weeks wash-out with a placebo run-in for the last 2 weeks; for patients with metformin monotherapy: 2 weeks placebo run-in only Double-blind treatment with BI 1356/placebo or open-label treatment with glimepiride for 12 weeks followed by 2 weeks follow-up after study drug termination. Metformin was administered in an unchanged dosage throughout the trial (including wash-out and placebo run-in phase).
Criteria for evaluation:	
Efficacy / clinical pharmacology:	HbA1c change from baseline, fasting plasma glucose change from baseline, absolute efficacy response in terms of HbA1c ≤7.0%
Safety:	Incidence and intensity of adverse events, withdrawal due to adverse events, physical examination and vital signs (blood pressure and pulse), 12-lead ECG, clinical laboratory assessments

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Statistical methods: Hierarchical testing of superiority hypotheses against placebo, starting with highest doses. Analysis of covariance with terms for treatment and HbA1c baseline (fixed effects) as covariate; descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

A total of 669 patients were enrolled in this trial. Of these, 336 patients (50.2%) were not randomised, mostly due to the violation of inclusion/exclusion criteria. A total of 333 patients were randomised into 1 of 5 treatment groups (1 mg, 5 mg, and 10 mg BI 1356; placebo; open-label glimepiride). Almost all of the randomised patients were white (98.5%). The mean age of the patients was 60.0 years, the mean baseline BMI was 31.9 kg/m^2. Generally, the demographic and baseline efficacy parameters were reasonably balanced across treatment groups. However, there were slight imbalances in gender and in the frequency of patients who were pre-treated with antidiabetic medication other than metformin. While overall 58.0% of the patients were male, the group receiving 10 mg of BI 1356 consisted only of 53.0% males compared with 62.0% and 63.1% in the placebo and glimepiride groups. Previous antidiabetic medication in addition to metformin was taken by only 28.1% and 29.7% of the patients in the glimepiride and 1 mg BI 1356 groups, respectively, whereas 32.9% of patients in the placebo group as well as 40.3% and 42.4% of the patients in the 5 mg and 10 mg BI 1356 groups were receiving previous antidiabetic therapy. The baseline values for HbA1c and fasting plasma glucose were reasonably balanced across treatment groups; the mean baseline HbA1c value was in the range of 8.2% to 8.5%; the mean fasting plasma glucose level ranged between 179.9 mg/dL and 189.3 mg/dL at baseline.

The primary endpoint for this study was the change in HbA1c from baseline to week 12 which was analysed using ANCOVA that included a covariate for baseline HbA1c. The adjusted mean changes in HbA1c from baseline were –0.15% for 1 mg BI 1356, –0.48% for 5 mg BI 1356, and –0.42% for 10 mg BI 1356). All doses of BI 1356 were significantly different from placebo in terms of HbA1c reduction. The mean differences to placebo were –0.40% for 1 mg BI 1356,–0.73% for 5 mg BI 1356, and –0.67% for 10 mg BI 1356. After adjustment for previous antidiabetic therapy status, the difference in HbA1c to placebo was –0.39% for 1 mg BI 1356, –0.75% for 5 mg BI 1356, and –0.73% for 10 mg BI 1356. The slightly greater placebo-corrected HbA1c reduction seen in patients treated with glimepiride (–0.93%) was expected due to the substantial

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	short-term effect of sulfonylureas. The adjusted mean change in fasting plasma glucose from baseline to week 12 was statistically different from placebo for all of the 3 doses of BI 1356. The mean differences to placebo were –19.2 mg/dL for 1 mg BI 1356, –34.7 mg/dL for 5 mg BI 1356, and –29.0 mg/dL for 10 mg BI 1356. There was a dose response relationship for DPP-4 inhibition. In the treatment groups 5 mg and 10 mg BI 1356, 87% and 93% of the patients with available DPP-4 data showed a DPP-4 inhibition of ≥80% at trough at week 12, while only 8% of the patients in the 1 mg BI 1356 group reached this target.
Safety results:	Out of the 333 randomised patients, 268 patients received double-blind treatment with BI 1356 or placebo. A total of 65 patients received open-label treatment with glimepiride. The mean treatment duration with BI 1356 and glimepiride was 80.2 days and 83.7 days, respectively. Overall, 149 patients (44.7%) experienced adverse events during study treatment. The most commonly reported adverse events were nasopharyngitis (7.5%), diarrhoea (3.3%), and nausea (3.0%). The incidence of these events was comparable for all treatment groups, i.e. treatment with BI 1356, glimepiride, and placebo. No dose relationship to BI 1356 of any adverse event was observed and no case of hypoglycaemia was reported with BI 1356 treatment. Adverse events that were deemed drug-related were reported for 16 patients (8.1%) receiving any dose of BI 1356, 8 patients (12.3%) treated with glimepiride, and 4 patients (5.6%) receiving placebo. Adverse events considered drug-related that occurred in more than 1 patient in any treatment group were diarrhoea (2 patients receiving 5 mg BI 1356, 1 patient receiving placebo), nausea (2 patients receiving 5 mg BI 1356, 1 patient receiving 10 mg BI 1356, 1 patient receiving placebo), dyspepsia (2 patients receiving glimepiride, 1 patient receiving 5 mg BI 1356), and hypoglycaemia (3 patients receiving glimepiride). Adverse events that led to discontinuation of study medication were experienced by 11 patients (5.6%) receiving BI 1356, 3 patients (4.6%) receiving glimepiride, and 2 patients (2.8%) receiving placebo. Adverse events leading to discontinuation that affected more than 1 patient were increased blood glucose levels (4 patients), nausea (2 patients), fatigue (2 patients), and worsening of diabetes mellitus (2 patients). A total of 10 patients (3.0%) experienced serious adverse events during the randomised treatment phase. None of these events was

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	considered drug-related by the investigators. The incidence of serious adverse events in patients treated with BI 1356 was higher than in patients in the placebo group (4.1% vs. 1.4%). This imbalance was mainly due to the occurrence of cardiac serious adverse events. However, due to the small number of patients investigated, this observation was not considered as suggestive for an increased cardiac risk in patients treated with BI 1356. During the trial period, 3 patients had laboratory abnormalities reported as drug-related adverse events that led to premature discontinuation of trial medication. One of these abnormalities (blood amylase increased >2 times upper limit of normal) was considered to be possibly related to treatment with BI 1356, the other 2 abnormalities (decreased white blood cell count and hypoglycaemia) were regarded as possibly related to treatment with glimepiride. There were no serious adverse events due to laboratory abnormalities. The incidence of possibly clinically significant laboratory abnormalities was generally low with the exception of glucose, triglyceride, uric acid, total cholesterol, and potassium levels. Possibly clinically significant increases in glucose levels were seen in 37 patients. These increases were more frequently seen in patients in the placebo group, who were treated only with metformin, than in patients additionally treated with BI 1356 or glimepiride. Triglyceride, uric acid, total cholesterol, and potassium levels were possibly clinically significantly increased in 24, 13, 9 and 9 patients, respectively. The incidence of these increases was reasonably comparable across all treatment groups. Concerning vital signs and ECG, there were no safety issues for any of the treatments.
Conclusions:	This study demonstrated that all administered doses of BI 1356 (1 mg, 5 mg, and 10 mg) were superior to placebo in terms of reduction of mean HbA1c and fasting plasma glucose levels after 12 weeks of treatment. The mean differences in HbA1c to placebo were –0.40%, –0.73%, and –0.67% for 1 mg, 5 mg, and 10 mg BI 1356, respectively. Both the 5 mg and 10 mg doses, but not the 1 mg dose, reached DPP-4 inhibition of 80% or more at trough in more than 80% of the patients. Overall, treatment with 1 mg, 5 mg, and 10 mg BI 1356 was well tolerated and the good safety/tolerability assessment for BI 1356 was confirmed.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement patient disposition results and the results for 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
HbA1c change from baseline at week 12 (Primary Endpoint)	Table 15.2.1.1: 1
Fasting Plasma Glucose (FPG) change from baseline after 12 weeks (Secondary Endpoint)	Table 15.2.2.1.1: 1
Frequency of absolute responders (HbA1c <= 7.0%) at week 12 (Secondary Endpoint)	Table 15.2.2.2.2: 2 Table 15.2.2.2.2: 1
Adverse Events	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

Treatment analysis: All patients

	Placebo N (%)	BI1356 1 mg N (%)	BI1356 5 mg N (%)	BI1356 10 mg N (%)	Glimepiride N (%)	Total N (%)
Enrolled						669
Not entered/randomised						336
Entered/randomised	71	65	66	66	65	333
Not treated	0	0	0	0	0	0
Treated	71 (100.0)	65 (100.0)	66 (100.0)	66 (100.0)	65 (100.0)	333 (100.0)
Not prematurely discontinued from trial medication	57 (80.3)	52 (80.0)	56 (84.8)	60 (90.9)	61 (93.8)	286 (85.9)
Prematurely discontinued from trial medication	14 (19.7)	13 (20.0)	10 (15.2)	6 (9.1)	4 (6.2)	47 (14.1)
Adverse event	1 (1.4)	5 (7.7)	3 (4.5)	2 (3.0)	3 (4.6)	14 (4.2)
AE study dis. worse	0 (0.0)	3 (4.6)	0 (0.0)	1 (1.5)	0 (0.0)	4 (1.2)
AE other dis. worse	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)	2 (0.6)
AE other	1 (1.4)	1 (1.5)	3 (4.5)	1 (1.5)	2 (3.1)	8 (2.4)
Lack of efficacy	10 (14.1)	4 (6.2)	3 (4.5)	3 (4.5)	0 (0.0)	20 (6.0)
Non compl. protocol	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Lost to follow-up	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)	1 (1.5)	3 (0.9)
Refused cont. medica	1 (1.4)	4 (6.2)	2 (3.0)	0 (0.0)	0 (0.0)	7 (2.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.3)

Table 15.2.1.1: 1 Adjusted means for HbA1c change from baseline at week 12
FAS - LOCF

	Placebo	BI1356 1mg	BI1356 5mg	BI1356 10mg
Number of Patients	70	64	62	66
HbA1c [%]				
Adjusted mean change from baseline (SE)	0.25 (0.10)	-0.15 (0.10)	-0.48 (0.11)	-0.42 (0.10)
Difference to Placebo (SE)		-0.40 (0.14)	-0.73 (0.14)	-0.67 (0.14)
95% CI		(-0.68, -0.12)	(-1.01, -0.44)	(-0.95, -0.39)
P-value		0.0055	<.0001	<.0001

Means are adjusted for baseline HbA1c, treatment.

Table 15.2.2.1.1: 1 Adjusted means for FPG change from baseline at week 12
FAS - LOCF

	Placebo	BI1356 1mg	BI1356 5mg	BI1356 10mg
Number of Patients	68	63	62	66
Fasting blood plasma glucose level [mg/dL]				
Adjusted mean change from baseline (SE)	12.69 (4.26)	-6.53 (4.43)	-22.00 (4.46)	-16.32 (4.32)
Difference to Placebo (SE)		-19.22 (6.14)	-34.69 (6.17)	-29.01 (6.07)
95% CI		(-31.3, -7.13)	(-46.8, -22.5)	(-41.0, -17.1)
P-value		0.0020	<.0001	<.0001

Means are adjusted for baseline FPG, treatment.

Table 15.2.2.2.2: 2 Frequency of absolute responders (HbA1c <= 7.0%) at week 12
FAS - LOCF

Endpoint	Statistic*	Placebo	BI1356 1mg	BI1356 5mg	BI1356 10mg	Glimepiride
HbA1c <= 7.0%	Number of patients	70	64	62	66	64
	n (%)	1 (1.4)	10 (15.6)	9 (14.5)	14 (21.2)	20 (31.3)
	Odds ratio 95% CI		12.778 (1.586, 102.920)	11.717 (1.439, 95.374)	18.577 (2.367, 145.818)	31.364 (4.063, 242.088)

* Odds ratios are relative to placebo

Table 15.2.2.2.2: 1 Logistic regression of absolute responders (HbA1c <= 7.0%) at week 12
FAS - LOCF

Factor	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	Wald Chi-Sq	df	p-value
Treatment Group				14.868	4	0.0050
BI 1356 (1 mg) : Placebo	12.776	1.586	102.895	5.729	1	0.0167
BI 1356 (5 mg) : Placebo	11.715	1.439	95.351	5.292	1	0.0214
BI 1356 (10 mg) : Placebo	18.575	2.367	145.781	7.725	1	0.0054
Glimepiride : Placebo	31.360	4.063	242.028	10.921	1	0.0010

Table 15.3.2: 1 Adverse event overall summary - treated set

Treatment analysis: Treatment period + 30 days

	Placebo N (%)	BI1356 1 mg N (%)	BI1356 5 mg N (%)	BI1356 10 mg N (%)	Glimepiride N (%)	Post Study N (%)
Number of patients	71 (100.0)	65 (100.0)	66 (100.0)	66 (100.0)	65 (100.0)	333 (100.0)
Patients with any AE	33 (46.5)	25 (38.5)	32 (48.5)	30 (45.5)	29 (44.6)	1 (0.3)
Patients with severe AEs	2 (2.8)	4 (6.2)	1 (1.5)	2 (3.0)	1 (1.5)	0 (0.0)
Patients with investigator defined drug-related AEs	4 (5.6)	3 (4.6)	7 (10.6)	6 (9.1)	8 (12.3)	0 (0.0)
Patients with other significant AEs (according to ICH E3)	2 (2.8)	5 (7.7)	3 (4.5)	2 (3.0)	5 (7.7)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	2 (2.8)	6 (9.2)	3 (4.5)	2 (3.0)	3 (4.6)	0 (0.0)
Patients with serious AEs	1 (1.4)	3 (4.6)	1 (1.5)	4 (6.1)	1 (1.5)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	1 (1.4)	3 (4.6)	1 (1.5)	2 (3.0)	1 (1.5)	0 (0.0)
Prol.hospitalisation	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 10.0
Other significant AEs (according to ICH E3) includes only non serious AEs leading to discontinuation or dose reduction
MedDRA version 10.0 was used for reporting

Table 15.3.2: 1 Adverse event overall summary - treated set

Treatment analysis: Treatment period + 30 days

	Total BI N (%)
Number of patients	197 (100.0)
Patients with any AE	87 (44.2)
Patients with severe AEs	7 (3.6)
Patients with investigator defined drug-related AEs	16 (8.1)
Patients with other significant AEs (according to ICH E3)	10 (5.1)
Patients with AEs leading to discontinuation of trial drug	11 (5.6)
Patients with serious AEs	8 (4.1)
Fatal	0 (0.0)
Imm life-threatening	1 (0.5)
Disability/incap.	0 (0.0)
Req.hospitalisation	6 (3.0)
Prol.hospitalisation	2 (1.0)
Congenital anomaly	0 (0.0)
Other	1 (0.5)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 10.0
Other significant AEs (according to ICH E3) includes only non serious AEs leading to discontinuation or dose reduction
MedDRA version 10.0 was used for reporting