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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-007865-19	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 09 DEC 2009	**Trial No. / U No.:** 1218.37 / U09-2397-02	**Date of trial:** 18 JUL 2008 – 19 NOV 2008	**Date of revision:** 10 MAY 2010

Title of trial:	A 4-week, randomised, double blind, double dummy, placebo controlled, parallel group study comparing the influence of BI 1356 (5 mg) and sitagliptin (100 mg) administered orally once daily on various biomarkers in type 2 diabetic patients
Coordinating Investigator:	[redacted]
Trial sites:	Profil Institut für Stoffwechsel GmbH, Hellersbergstraße 9, 41460 Neuss, Germany Institut für Klinische Forschung und Entwicklung (ikfe), Parcusstraße 8, 55116 Mainz, Germany PAREXEL International GmbH, Institut für Klinische Pharmakologie, Klinikum Westend, Haus 18, Spandauer Damm 130, 14050 Berlin, Germany
Publication (reference):	Not applicable
Clinical phase:	IIa
Objectives:	To compare the effect of BI 1356 (5 mg) and sitagliptin (100 mg) on 24-hour glucose control with placebo in type 2 diabetic patients with inadequate glycaemic control. In addition, various pharmacodynamic variables (e.g. GLP-1, insulin, DPP-4 inhibition) were investigated.
Methodology:	Randomised, double-blind, double-dummy, placebo-controlled, 3 parallel groups, multiple centres.
No. of subjects:	
planned:	entered: 120
actual:	enrolled: 194 Treatment BI 1356: entered: 40 treated: 40 analysed (for primary endpoint): 39 Treatment sitagliptin: entered: 41 treated: 41 analysed (for primary endpoint): 40 Treatment placebo: entered: 40 treated: 40 analysed (for primary endpoint): 38

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Diagnosis and main criteria for inclusion:	Type 2 diabetes mellitus; age ≥ 18 and ≤ 80 years; treatment naïve or previous monotherapy with oral anti-diabetic agents; HbA_{1c} ≥6.5% to ≤10.0% at start of run-in period; BMI ≤ 40 kg/m^2 at screening visit
Test product:	BI 1356
dose:	5 mg tablet
mode of admin.:	Oral
batch no.:	B083000516
Reference therapy:	Placebo matching BI 1356
dose:	Tablet, dose not applicable
mode of admin.:	Oral
batch no.:	B083000517
Test product:	Sitagliptin
dose:	100 mg capsule (2 x 50 mg tablets, encapsulated)
mode of admin.:	Oral
batch no.:	B083000127
Reference therapy:	Placebo matching sitagliptin
dose:	Capsule, dose not applicable
mode of admin.:	Oral
batch no.:	B083000124
Duration of treatment:	2 week wash-out (only patients already treated with one oral anti-diabetic medication); 2 week placebo run-in phase; 4 week double-blind treatment with BI 1356, sitagliptin or placebo; 2 week follow-up phase

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Criteria for evaluation:

Efficacy / clinical pharmacology: Change from baseline in weighted mean glucose (WMG), change from baseline in the $AUEC_{0-2h}$ of GLP-1 after a meal tolerance test.

Pharmacodynamic responses to study drug administration for plasma glucose, active GLP-1, active and total GIP, insulin, C-peptide, glucagon, HbA_{1c}, fructosamine, 1,5 anhydroglucitol, and the inhibition of plasma DPP-4 activity.

Safety: Adverse event (AE) frequencies and severities, vital signs, 12-lead ECG, physical examination, and safety laboratory tests (haematology, clinical chemistry, and urinalysis).

Statistical methods: Testing of superiority hypothesis of BI 1356 versus placebo with an analysis of covariance for WMG change from baseline and GLP-1 change from baseline after 4 weeks with factors treatment and prior antidiabetic therapy and covariate baseline HbA_{1c}.
Descriptive statistics for secondary / exploratory endpoints and safety parameters.

Estimation of the insulin secretion rate (ISR) based on a deconvolution approach.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: In this trial 194 patients were enrolled, of whom 121 were randomised. The number of randomised patients was similarly distributed in the 3 participating centres. Of the randomised patients, 40 were treated with placebo, 40 were treated with 5 mg BI 1356, and 41 were treated with sitagliptin. Three patients (2.5% of total) withdrew from the study prematurely and were excluded from the PPS completers set, and the PD Set. These were 2 patients (placebo) who experienced hyperglycaemia and discontinued the trial due to lack of efficacy, and 1 patient (BI 1356) that was removed due to difficulty in obtaining blood samples.

The mean age of the patients was 61.1 years (SD 9.1), the youngest participant was 28 years of age and the oldest was 76 years of age. About half of the patients overall (52%) were aged 65 years or older. The mean body weight was 91.4 kg (SD 16.0), the mean height was 172.1 cm (SD 9.2), and the mean body mass index (BMI) was 30.8 kg/m^2 (SD 4.3).

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Overall, 98% of the patients were white; 1 patient was American Indian and 1 patient was African American. Values of demographic and other baseline characteristics were similarly distributed across treatment groups. A minor, not significant quantitative imbalance of mean baseline HbA_{1c} was noted, originating from a slightly lower baseline HbA_{1c} in the sitagliptin group. For the comparison between placebo and BI 1356, the difference of baseline HbA_{1c} was not significant. Baseline values for insulin, HOMA index for insulin resistance and for insulin secretion were variable within and across the treatment groups.

Primary endpoints

The primary endpoint of the study was the change from baseline in weighted mean glucose to day 28. Additionally, the change from baseline for GLP-1 $AUEC_{0-2h}$ following an MTT on day 28 was investigated as a primary endpoint. Assay sensitivity was established by demonstrating superiority of sitagliptin over placebo.

For both WMG and GLP-1 $AUEC_{0-2h}$, superiority of BI 1356 was shown with respect to placebo. For BI 1356, the placebo-corrected change from baseline of WMG after 4 weeks of treatment was −19.9 mg/dL (95% CI: −28.0 to −11.9; $p<0.0001$). The placebo-corrected change from baseline of GLP-1 after 4 weeks of treatment was 18.1 pmol*h /L (95% CI: 12.4 to 23.9; $p<0.0001$). Sensitivity analyses of the primary analysis confirmed the superiority of BI 1356 over placebo with regard to both primary endpoints.

Secondary endpoints

Secondary endpoints were the change from baseline in fasting plasma glucose to day 28 and the change from baseline for plasma glucose $AUEC_{0-3h}$ following an MTT on day 28. BI 1356 was shown to be superior to placebo in the analysis of both secondary endpoints. After 4 weeks of treatment with BI 1356, the placebo-corrected change from baseline of FPG was −10.8 mg/dL (95% CI: −20.4 to −1.2), and the placebo-corrected change from baseline of plasma glucose $AUEC_{0-3h}$ was −106.5 mg*h/dL (95% CI: −147.0 to −66.0). The reduction of the plasma glucose $AUEC_{0-3h}$ by BI 1356 was numerically greater than the reduction of the WMG; the time-normalised reduction in $AUEC_{0-3h}$ was 35.5 mg/dL and the reduction of WMG was 19.9 mg/dL.

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Safety results:	All 121 treated subjects who had received at least one dose of trial medication were included in the analysis of safety. A total of 39 subjects received a total dose of 140 mg of BI 1356 during the planned treatment period of 28 days. One patient received 5 mg BI 1356 for 1 day, but was removed from the trial due to difficulty in drawing blood samples in this patient. All 41 patients in the sitagliptin group received the planned dose of 100 mg for 28 days. During the treatment period, 43 patients (35.5%) experienced at least one treatment-emergent AE. Most of the AEs were of mild intensity, some were of moderate intensity and none of severe intensity. There were no AEs which leading to discontinuation, no protocol-defined significant AEs, no serious AEs (SAE), and no deaths reported during the trial. During the washout period, one patient experienced 2 SAEs (aggravated migraine and a panic attack that required hospitalisation). On treatment, the most frequently reported AE was headache, affecting a total of 12 patients (9.9%), of whom 3 patients (7.5%) were on treatment with placebo, 4 patients (10.0%) on treatment with BI 1356, and 5 patients (12.2%) on treatment with sitagliptin. Drug-related AEs, as defined by the investigator, occurred in a total of 8 patients (6.6%): 1 patient (2.5%) in the placebo group (upper abdominal pain); 2 patients (5%) in the BI 1356 group (headache and hyperhidrosis), and 5 patients (12.2%) in the sitagliptin group (headache [2 patients], hot flush, abdominal distention, rhinorrhoea, and dry mouth). Overall, the safety laboratory data and the assessment of vital signs revealed no changes of clinical relevance and that BI 1356 was overall well-tolerated.
Conclusions:	In summary, the results demonstrate that treatment with 5 mg BI 1356 is superior to placebo in achieving effective 24-hour glycaemic control in terms of reduction of weighted mean glucose, and prolongation of the presence of GLP-1 in plasma via DPP-4 inhibition. The assessment of safety revealed no changes of clinical relevance and BI 1356 was generally well-tolerated.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the results for the secondary endpoints. Note that not all 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**
Adjusted FPG (mg/dL) mean change from baseline at day 28	Table 15.5.2.1.1: 1
Adjusted glucose $AUEC_{(0-3)}$ (mg*h/dL) mean change from baseline at day 28	Table 15.5.2.2.1: 1

Table 15.5.2.1.1: 1 Adjusted means for FPG change from baseline at day 28
PD-set (BI-Pbo)

FPG [mg/dL]

	Placebo	BI 1356
Number of patients with endpoint data	38	39
Baseline (Day -1)		
Mean (SE)	169.6 (4.2)	166.6 (4.5)
Day 28		
Mean (SE)	170.7 (4.9)	157.0 (4.7)
Change from baseline		
Mean (SE)	1.1 (2.8)	-9.6 (4.1)
Adjusted** mean (SE)	-0.1 (3.6)	-10.9 (3.5)
Comparison vs. Placebo		
Adjusted** mean (SE)		-10.8 (4.8)
95% Confidence interval		(-20.4, -1.2)
p-value		0.0283

Source data: Appendix 16.1.9.3, Statdoc 1.3.1 stat\pd15_fpg.sas 24AUG2009
** adjusted for HbA1c baseline, treatment, prior use of antidiabetic agents and baseline of endpoint

Table 15.5.2.2.1: 1 Adjusted means for glucose AUEC(0-3h) change from baseline at day 28
PD-set (BI-Pbo)

Glucose AUEC MTT0-3h [mg*h/dL]

	Placebo	BI 1356
Number of patients with endpoint data	38	39
Baseline (Day -1)		
Mean (SE)	722.0 (22.5)	728.4 (25.1)
Day 28		
Mean (SE)	743.3 (24.7)	634.7 (22.6)
Change from baseline		
Mean (SE)	21.3 (14.5)	-93.7 (16.4)
Adjusted** mean (SE)	8.1 (15.1)	-98.4 (14.7)
Comparison vs. Placebo		
Adjusted** mean (SE)		-106.5 (20.3)
95% Confidence interval		(-147.0, -66.0)
p-value		<0.0001

Source data: Appendix 16.1.9.3, Statdoc 1.4.1 stat\pd15_glu.sas 24AUG2009
** adjusted for HbA1c baseline, treatment, prior use of antidiabetic agents and baseline of endpoint