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.:** 2008-003118-86	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure synopsis date: 12-JUN-2014	**Trial No. / U No.:** 1218.35 / U10-3206-01	**Date of trial:** 11 December 2008 – 14 January 2010	**Date of revision :** Not applicable

Title of trial:	A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 18 weeks in Type 2 diabetic patients with insufficient glycaemic control (HbA1c 7.0-10%) despite background therapy with a sulphonylurea drug
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre Study with 45 centres in 7 countries (Argentina, Hungary, India, Japan, Poland, Russia, USA)
Publication (reference):	Lewin AJ, Arvay L, Liu D, Patel S, Eynatten M von, Woerle HJ. Clin Ther 2012;34(9): 1909-1919.
Clinical phase:	III
Objectives:	To investigate the efficacy, safety and tolerability of linagliptin 5 mg versus placebo administered for 18 weeks with a sulphonylurea background therapy in patients with Type 2 diabetes mellitus and insufficient glycaemic control.
Methodology:	Randomised, double-blind, and placebo controlled, parallel group study comparing linagliptin (5 mg) to placebo as add-on therapy to the study patients' anti-diabetic sulphonylurea drug over an 18-week treatment period. The randomisation was stratified based on prior anti-diabetic drugs and the screening HbA1c value at the beginning of the placebo Run-in Period.
No. of subjects:	
planned:	entered: 255 enrolled: 450
actual:	Linagliptin 5 mg: entered: 161 treated: 161 analysed (for primary endpoint): 158 Placebo: entered: 84 treated: 84 analysed (for primary endpoint): 82

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Diagnosis and main criteria for inclusion:	Patients ≥18 and <80 years with Type 2 diabetes with insufficient glycaemic control (glycosylated haemoglobin [HbA_{1c}] ≥7.0% and ≤10%) despite therapy with a sulphonylurea drug.
Test product:	Linagliptin
dose:	5 mg once daily
mode of admin.:	Tablet, oral
batch no.:	B083000516 B083000561 B083000562
Reference therapy:	Placebo
dose:	Matching placebo control as add-on to sulphonylurea drug
mode of admin.:	Tablet, oral
batch no.:	B083000703
Duration of treatment:	A 4-week Wash-out Period followed by a two-week open-label Placebo Run-in Period, for patients pre-treated with one oral anti-diabetic agent in addition to a sulphonylurea drug or two weeks Placebo Run-in for patients pre-treated with a sulphonylurea drug monotherapy; 18 weeks double-blind treatment followed by 1-week follow-up after study drug termination. The study patients' sulphonylurea drug was administered during the entire trial duration (including Wash-out and Placebo Run-in Period) in an unchanged dosage.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the change from baseline in HbA_{1c} after 18 weeks of treatment. Important secondary endpoints were the change from baseline in Fasting Plasma Glucose (FPG) after 18 weeks of treatment and the occurrence of treat-to-target response (i.e., an HbA_{1c} during treatment of <7.0% or <6.5%).

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Safety:	Incidence and intensity of adverse events (AE) including SAEs, withdrawals due to AEs, physical examination, 12-lead electrocardiogram (ECG), clinical laboratory parameters and vital signs.
Statistical methods:	Primary endpoint: Testing of superiority hypothesis versus placebo using analysis of covariance (ANCOVA) for HbA_{1c} change from baseline after 18 weeks with covariates: treatment, prior use of anti-diabetic agents, and baseline HbA_{1c}. Secondary and other endpoints: ANCOVA (exploratory); logistic regression and Kaplan-Meier analysis for use of rescue medication Safety endpoints: Descriptive statistics; logistic regression and Kaplan-Meier analysis for hypoglycaemic events

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:	A total of 471 patients were enrolled; 280 patients entered the 2-week Placebo Run-in Period; 245 were randomised in a 1:2 ratio to receive treatment with either placebo (84 patients) or linagliptin 5 mg (161 patients). All randomised patients were treated. Of the treated patients, 228 (93.1%) completed treatment with trial medication; 17 patients (6.9%) prematurely discontinued study treatment (7 [8.3%] placebo; 10 [6.2%] Linagliptin) most frequently due to adverse events. Overall, the demographic data were balanced between the treatment groups. There were more men in the placebo group (61.9%) than in the linagliptin group (47.8%). Apart from 1 American Indian / native Alaskan patient in each arm, the patient population in combined treatment groups consisted of Asian (48.6%), White (43.7%) and Black patients (6.9%). 17.1% of the patients were of Hispanic / Latino origin. The mean age was 56.9 years. The placebo group comprised of more patients <65 years of age (83.3%) compared to the linagliptin group (74.5%). Overall the majority of patients had a baseline eGFR (based on MDRD staging) of ≥90 mL/min (53.9%) or 60 to <90 mL/min (38.4%). There was 1 patient in each treatment group with severe renal impairment (eGFR <30 mL/min) at baseline. Primary endpoint: There were 82 patients in the placebo group and 158 patients in the linagliptin group included in the FAS. The FAS included all treated patients with a baseline and at least one on-treatment HbA_{1c}

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measurement available. All efficacy analyses were based on the FAS. The primary endpoint was the change from baseline in HbA_{1c} (HbA_{1c} after 18 weeks of treatment). The treatment difference between linagliptin (n=158) and placebo (n=82), calculated as the adjusted mean change in HbA_{1c} from baseline at Week 18, was -0.47% (95% CI -0.70, -0.24), showing superiority of linagliptin over placebo (p<0.0001). Sensitivity analyses were consistent with the results observed for the primary analysis. From baseline to Week 18, across visits, the difference between the adjusted means of HbA_{1c} (Linagliptin - placebo) was observed to be statistically significant (p<0.0001). The adjusted mean treatment differences ranged from -0.41% at Week 6 to -0.47% at Week 18. Subgroup analyses for the unadjusted mean change in HbA_{1c} from baseline showed a consistent treatment effect across the different subgroups. A statistically significant difference in HbA_{1c} change from baseline was observed over time at Weeks 6, 12 and 18 (p<0.0001).

Secondary endpoints: The difference between the two treatment groups in the adjusted mean change in FPG from baseline at 18 weeks was -6.4 mg/dL (p=0.2406) for the FAS population. Sensitivity analyses confirmed the observed results. From baseline to Week 12, the difference between the adjusted means of FPG (linagliptin - placebo) was statistically significant (p=0.0105). The differences between the treatment groups at Weeks 6 and 18 were similar and not statistically different. The treat-to-target efficacy analysis for patients with baseline HbA_{1c} ≥7.0% demonstrated that 3.7% of the patients in the placebo group and 15.2% of the patients in the linagliptin group achieved HbA_{1c} <7.0%. The odds for patients with a baseline HbA_{1c} of ≥7.0% to have a response of HbA_{1c} reduced to <7.0% at 18 weeks was 6 times greater for patients treated with linagliptin when compared to placebo (odds ratio = 6.466, p=0.0065). For patients with baseline HbA_{1c} ≥6.5%, 2.4% of the patients in the placebo group and 5.7% of the patients in the linagliptin group achieved HbA_{1c} <6.5%. Overall, a greater frequency of patients in the linagliptin group had an HbA_{1c} reduction of at least 0.5%. A reduction of at least 0.5% in HbA_{1c} was seen with more frequency than in patients with a greater baseline HbA_{1c} ([≥9.0%: 34.5% placebo; 66.1% linagliptin]; [8.0% to <9.0%: 14.3% placebo; 54.3% linagliptin]) than among patients with lower

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	baseline HbA_{1c} ([7.0% to <8.0%: 16.7% placebo; 50.0% linagliptin]. The odds of achieving an HbA_{1c} reduction of at least 0.5% at 18 weeks was about 5 times greater for patients treated with linagliptin than in patients treated with placebo (odds ratio = 5.125, p<0.0001). Other endpoints: The proportion of patients requiring rescue therapy was twice as great for placebo compared to linagliptin (15.9% of patients in the placebo group versus 7.6% of patients in the linagliptin group. The odds of requiring rescue therapy was about 3 times less for patients treated with linagliptin compared to those taking placebo (odds ratio = 0.398, p = 0.0350). There was no change in body weight or waist circumference from baseline to Week 18 for either treatment group. No differences between the treatment groups were observed for EQ-5D or HCRU. Greater improvement in all categories was observed for DTSQ change from baseline in the linagliptin group compared to the placebo group. Biomarkers: Statistically significant and relevant treatment differences were observed for HOMA-IR (p= 0.0146), when comparing the two treatments. No significant differences between the treatment groups in adjusted mean change from baseline to Week 18 were observed for HOMA-%B or disposition index.
Safety results:	The mean exposure of patients to treatment was 121 days (placebo) and 124 days (linagliptin). Median exposure was 127 days for both groups. Adverse Events (AEs): Overall, the frequency of AEs was similar for the two groups: 68 patients (42.2%) in the linagliptin group and 36 patients (42.9%) in the placebo group. AEs of severe intensity were reported for 4 patients (2.5%) in the linagliptin group and none in the placebo group; otherwise, all AEs were of mild or moderate intensity. The most frequently reported system organ class (SOC) was metabolism and nutrition disorders (21.4% placebo; 16.1% linagliptin) followed by infections and infestations (4.8% placebo; 12.4% linagliptin). Nasopharyngitis (1.2% placebo; 4.3% linagliptin) was the most frequently reported preferred term in this SOC. Skin disorders have been reported for other DPP-4 inhibitors and were of particular interest. AEs based on the SOC 'skin and subcutaneous tissue disorders' were reported in 4 patients (2.5%) in the linagliptin group and 1 patient (1.2%) in the placebo group. In the SOCs blood and lymphatic system disorders, anaemia was

reported for 1 patient (0.6%) in the linagliptin group and 1 patient (1.2%) in the placebo group. For the AE SOC of cardiac disorders, in the linagliptin treatment group there was one reported event each of cardio-respiratory arrest leading to sudden death, myocardial infarction, and supraventricular tachycardia. These were SAEs and are included in the SAE summary, below. There were no AEs in the SOC of cardiac disorders reported in the placebo group.

Investigator-reported cases of protocol-defined hypoglycaemia (categories of hypoglycaemia and other preferred terms related to symptoms of hypoglycaemia) was reported by 4 patients (4.8%) in the placebo group and 9 patients (5.6%) in the linagliptin group. None of the episodes was assessed as severe. A total of 2 patients, both in the linagliptin group, experienced potential cardiovascular events that qualified for adjudication by an independent external Clinical Event Committee (CEC). One (1) patient was confirmed with unstable angina and one patient was confirmed with sudden death. The sudden death is included in the SAE summary below.

There were 4 patients (2.5%) in the linagliptin treatment group and 3 patients (3.6%) in the placebo group with AEs leading to discontinuation of study medication. In the linagliptin group, 1 patient was discontinued due to pyelonephritis and 1 patient due to hepatic enzyme increased; neither AE was assessed by the investigator as related to study medication. In the linagliptin group 1 patient was discontinued due to sinusitis and 1 patient due to hypoglycaemia; both AEs were assessed by the investigator as related to study medication. Investigator defined drug-related AEs occurred in 9.5% of patients in the placebo group, and in 8.1% of patients in the linagliptin group.

The overall frequency of patients reported with protocol-defined AEs of special interest, assessed via ‘standard MedDRA (medical drug dictionary for drug regulatory affairs) queries,’ was 2 patients (1.2%) in the linagliptin group who were reported with significant renal adverse events (renal failure acute, reported as an SAE in the SAE summary below, and renal impairment); 1 patient (0.6%) in the linagliptin group with a significant hepatic adverse event (elevated hepatic enzymes) with treatment discontinued but assessed by the investigator as not related to study medication. 2 patients (1.2%) in the linagliptin group were identified with possible hypersensitivity reactions: 1 patient sustained a cardiorespiratory arrest, reported as an SAE in the SAE

summary below and which was fatal and adjudicated as sudden death with no evidence of a hypersensitivity reaction. A second patient experienced urticaria which was not considered serious but a protocol defined significant event. Neither the sudden death nor urticaria events were considered by the investigator to be related to study medication. There were no patients in the placebo group reported with significant renal, hepatic or hypersensitivity reactions.

Serious adverse events (SAEs) were reported for 5 patients (3.1%) in the linagliptin group and 1 patient (1.2%) in the placebo group. For patients in the linagliptin group, SAEs by SOC were cardiac disorders (1.9%), eye disorders (0.6%), hepatobiliary disorders (0.6%), infections and infestations (0.6%), and renal and urinary disorders (0.6%). For the patient in the placebo group, the SAE by SOC was a nervous system disorder (1.2%). None of the SAEs in either treatment group was considered to be related to study medication by the investigator.

Laboratory parameters and vital signs: Laboratory parameters measured (haematology, clinical chemistry, and urinalysis) were similar for the two treatment groups. Few patients were reported with possibly clinically significant abnormalities. No differences were observed between the treatment groups in changes from baseline in lipid parameters (cholesterol, LDL, HDL, plasma triglycerides) to Week 18. There were no patients with liver function abnormalities meeting criteria for Hy's law cases in this study. There were no apparent differences in renal function when comparing the treatments groups. No differences between the treatment groups were observed for changes from baseline in blood pressure or pulse rate.

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Conclusions:

A statistically significant and clinically relevant reduction in the change from baseline in HbA_{1c} (HbA_{1c} after 18 weeks of treatment) was observed for linagliptin compared to placebo. The treatment difference met the pre-defined criteria for superiority.

The reported safety results relating to overall and drug-related AEs were comparable between linagliptin and placebo. The incidence of hypoglycaemic events during treatment with linagliptin was comparable to placebo and all episodes were mild. No change in body weight or waist circumference was observed.

In this study in patients with Type 2 diabetes treated with a sulphonylurea and with insufficient glycaemic control, linagliptin was effective in reducing HbA_{1c} and was safe and well tolerated when compared to placebo.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for the secondary endpoints of the trial. 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**
FPG (mg/dL) mean change from baseline over time to week 18	Table 15.2.2.1: 6
Patients achieving HbA_{1c} <6.5% at week 18 for patients with baseline HbA_{1c} ≥6.5%	Table 15.2.2.3: 1
Patients achieving HbA_{1c} lowering by ≥0.5% at Week 18	Table 15.2.2.4: 2
HbA_{1c} (%) change from baseline over time to week 18	Table 15.2.1.2.1: 5

Table 15.2.2.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time - FAS (LOCF)

	Placebo			Linagliptin			Difference Linagliptin - Placebo				
	N	Adj* mean	SE	N	Adj* mean	SE	Adj* mean	SE	95% CI LL	95% CI UL	p-value
Baseline (unadjusted means)	78	171.0	5.3	155	180.1	4.0					
Change from baseline at Week 6	78	-7.6	3.8	155	-13.5	2.7	-5.9	4.6	-14.9	3.1	0.1970
Change from baseline at Week 12	78	4.1	4.7	155	-10.3	3.4	-14.5	5.6	-25.5	-3.4	0.0105
Change from baseline at Week 18	78	-1.8	4.5	155	-8.2	3.3	-6.4	5.5	-17.2	4.3	0.2406

* Model includes treatment, baseline HbA1c and baseline FPG, number of previous antidiabetic drugs

Table 15.2.2.3: 1 Logistic regression of HbA1c < 6.5% at Week 18 - FAS patients with baseline HbA1c >= 6.5% (NCF)

Factor	Odds ratio	95% CI LL	95% CI UL	Wald Chi-Sq	df	p-value
Treatment Group						
Linagliptin : Placebo	2.653	0.515	13.652	1.362	1	0.2431
Baseline HbA1c						
Odds ratio per 1% increase	0.171	0.060	0.490	10.822	1	0.0010
Number of prior antidiabetics drugs				0.006	1	0.9399
Two : One	0.000	0.000	3.78E131	0.006	1	0.9399

The number of patients with HbA1c < 6.5% at Week 18 is small, and there is possibly a quasi-complete separation of data points. The estimates and statistical test may not be reliable.

Table 15.2.2.4: 2 Number of patients with HbA1c lowering by 0.5% at Week 18 - FAS (NCF)

	Placebo (N=82)			Linagliptin (N=158)		
	HbA1c<0.5%			HbA1c<0.5%		
	No	Yes	Total	No	Yes	Total
Baseline HbA1c (categorical) [N (%)]						
N(non-missing)	64 (78.0)	18 (22.0)	82 (100.0)	67 (42.4)	91 (57.6)	158 (100.0)
<7.0%	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	2 (100.0)
7.0% to <8.0%	15 (83.3)	3 (16.7)	18 (100.0)	15 (50.0)	15 (50.0)	30 (100.0)
8.0% to <9.0%	30 (85.7)	5 (14.3)	35 (100.0)	32 (45.7)	38 (54.3)	70 (100.0)
>=9.0%	19 (65.5)	10 (34.5)	29 (100.0)	19 (33.9)	37 (66.1)	56 (100.0)

Table 15.2.1.2.1: 5 Adjusted means for HbA1c (%) change from baseline over time in mixed model repeated measurements analysis - FAS (OC)

	Placebo Mean (SE)	Linagliptin Mean (SE)	Difference (Linagliptin - Placebo) Mean (CI)	p-value
HBA1C				
Baseline (unadjusted means)	8.60 (0.08)	8.61 (0.07)		
Week 6	-0.02 (0.07)	-0.43 (0.05)	-0.41 (-0.585,-0.230)	<0.0001
Week 12	-0.11 (0.09)	-0.61 (0.07)	-0.50 (-0.720,-0.276)	<0.0001
Week 18	-0.08 (0.10)	-0.55 (0.07)	-0.47 (-0.716,-0.226)	0.0002

ANCOVA model with treatment, continuous baseline HBA1C, prior OADs, week repeated within patients, week by treatment interaction.