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: Not applicable		**EudraCT No.:** 2007-002448-10	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 JAN 2010	**Trial No. / U No.:** 1218.16 / U10-1103-04	**Dates of trial:** 15 FEB 2008 – 06 MAY 2009	**Date of revision:** 15 MAR 2011

Title of trial:	A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycaemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multi-national, multi-centre trial: 66 trial sites in 11 countries (Croatia, India, Italy, Israel, Malaysia, Poland, Romania, Slovakia, Ukraine, Thailand, The Netherlands)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the efficacy, safety, and tolerability of linagliptin 5 mg versus placebo administered for 24 weeks as monotherapy to patients with type 2 diabetes mellitus and insufficient glycaemic control.
Methodology:	Randomised, placebo-controlled, double-blind, parallel-group comparison of 2 groups over 24 weeks. Before randomisation, patients pre-treated with one oral antidiabetic agent underwent a washout period of 6 weeks that included a placebo run-in period during the last 2 weeks of the washout period; patients not previously treated with an oral antidiabetic agent performed a 2-week placebo run-in period.
No. of patients:	
planned:	Entered: 450
actual:	Enrolled: 935
	Linagliptin 5 mg Entered: 336 treated: 336 analysed (for primary endpoint): 333
	Placebo Entered: 167 treated: 167 analysed (for primary endpoint): 163

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Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus and insufficient glycaemic control either drug naïve or despite therapy with one oral antidiabetic agent (patients undergoing washout of previous antidiabetic medication: 6.5% ≤ glycosylated haemoglobin [HbA_{1c}] ≤9.0%; patients not undergoing washout of previous antidiabetic medication: 7.0% ≤ HbA_{1c} ≤10.0%); age ≥18 and ≤80 years; body mass index (BMI) ≤40 kg/m^2
Test product:	Linagliptin
dose:	5 mg once daily
mode of admin.:	Tablet, oral
batch no.:	B071001951 and B071003944
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Tablet, oral
batch no.:	B071003943 and 575992
Duration of treatment:	6-week washout period including placebo run-in during the last 2 weeks (patients pre-treated with one oral antidiabetic agent) or 2-week placebo run-in (patients not previously treated with an oral antidiabetic agent); 24-week treatment period; 1-week follow-up period
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. Important secondary endpoints were the change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment and the occurrence of treat-to-target response (i.e. HbA_{1c} on treatment <7.0% or <6.5%).
Safety:	Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory parameters.

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Statistical methods:

Primary endpoint: Testing of superiority hypothesis versus placebo with an analysis of covariance (ANCOVA) with treatment and previous antidiabetic therapy as factors and baseline HbA_{1c} as covariate

Secondary and other endpoints: ANCOVA (exploratory); for use of rescue medication logistic regression and Kaplan-Meier analysis

Safety endpoints: descriptive statistics; for hypoglycaemic events logistic regression and Kaplan-Meier analysis

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

A total of 935 patients were enrolled into this study, out of these 503 patients were randomised in a 1:2 ratio to either placebo (167 patients) or linagliptin (336 patients). The main reason for non-randomisation was inclusion or exclusion criteria not met (38.2%). All of the randomised patients were treated. Of the treated patients, 6.6% discontinued prematurely. The most frequent reasons for discontinuation were due to adverse events (1.8%), refusal to continue trial medication (2.0%), and other reason (1.8%).

Overall, the demographic profile was balanced between the treatment groups. Nearly half of the population was male (48.3%). Apart from one American Indian/native Alaskan patient in the placebo arm, the patient population in both treatment groups consisted only of Asian (46.1%) and White patients (53.7%). In general, the placebo group (83.8%) comprised a numerically higher proportion of younger patients (<65 years) than the linagliptin group (76.8%), and conversely the linagliptin group consisted of more patients aged 65 to 74 years (21.1%) or 75 years or older (2.1%) than the placebo group (15.6% and 0.6%, respectively). In both treatment groups, the majority of patients had either normal renal function (estimated glomerular filtration rate [eGFR] based on modification of diet in renal disease [MDRD] staging ≥90 mL/min; 43.1%) or mild renal impairment (eGFR 60 to <90 mL/min; 49.3%). The total percentage of patients with moderate renal impairment (eGFR 30 to <60 mL/min) was 3.6%. There were no patients with severe renal impairment (eGFR <30 mL/min).

Primary endpoint

163 patients of the placebo group and 333 patients of the linagliptin group were included in the full analysis set (FAS). The FAS was a subset of the treated set

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including all patients who had a baseline and at least one on-treatment HbA_{1c} measurement available. All efficacy analyses were based on the FAS.

Superiority of linagliptin (n = 333) over placebo (n = 163) was demonstrated for the primary endpoint of change in HbA_{1c} from baseline at Week 24. The treatment difference between linagliptin and placebo, calculated as the adjusted mean change in HbA_{1c} from baseline at Week 24, was -0.69% (standard error [SE] 0.08; 95% confidence interval -0.85, -0.53; $p<0.0001$; FAS). Sensitivity analyses confirmed the results observed for the primary endpoint. From baseline to Week 24, 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 -0.46% (SE 0.06) at Week 6 to -0.69% (SE 0.08) at Week 24. Subgroup analyses for the unadjusted mean change in HbA_{1c} from baseline showed a consistent treatment effect across the different subgroups. A significant interaction with treatment was shown for race ($p = 0.0190$) and country ($p = 0.0098$).

Secondary endpoints

The difference between the 2 treatment groups in the adjusted mean change in FPG from baseline at 24 weeks was -23.3 mg/dL (SE 3.6; $p<0.0001$) in favour of linagliptin (FAS). Sensitivity analyses confirmed the observed results. From baseline to Week 24, across visits, the difference between the adjusted means of FPG (linagliptin - placebo) was statistically significant ($p<0.0001$). Concerning the treat-to-target efficacy response, among patients with baseline HbA_{1c} ≥7.0%, 11.6% of the patients in the placebo group and 25.2% 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 24 weeks was almost 3 times higher for patients treated with linagliptin compared to placebo (odds ratio = 2.869, $p = 0.0006$). Among patients with baseline HbA_{1c} ≥6.5%, 4.9% of the patients in the placebo group and 10.6% of the patients in the linagliptin group achieved HbA_{1c} <6.5%. The odds for patients with a baseline HbA_{1c} of ≥6.5% to have a response of HbA_{1c} reduced to <6.5% at 24 weeks was more than 2 times higher for patients treated with linagliptin compared to placebo (odds ratio = 2.436, $p = 0.0323$). Overall, a higher frequency of patients in the linagliptin group had a HbA_{1c} reduction of at least 0.5%. A reduction of at least 0.5% in HbA_{1c} was seen at a higher frequency among patients with higher baseline HbA_{1c} ([≥9.0%: 20.8% placebo; 58.2%

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	linagliptin]; [8.0% to <9.0%: 26.4% placebo; 55.6% linagliptin]) than among patients with lower baseline HbA_{1c} ([7.0% to <8.0%: 15.7% placebo; 40.8% linagliptin]; [<7.0%: 6.3% placebo; 29.6% linagliptin]). The odds of achieving a HbA_{1c} reduction of at least 0.5% at 24 weeks was about 4 times higher for patients treated with linagliptin compared to placebo (odds ratio = 4.243, p<0.0001). The difference in the adjusted mean change from baseline in 2hPPG at Week 24 between the 2 treatment groups was -58.38 mg/dL (p<0.0001), in favour of linagliptin. *Other endpoints* A higher proportion of patients in the placebo group (20.9%) received rescue medication than in the linagliptin group (10.2%). The odds of requiring rescue therapy was about 3 times lower for patients treated with linagliptin compared to those taking placebo (odds ratio = 0.316, p = 0.0002). There was no significant change in body weight from baseline to 24 weeks between the 2 treatment groups. *Biomarker, pharmacokinetic, and pharmacodynamic results* Linagliptin trough levels in patients with mild or moderate renal impairment were comparable to patients with normal renal function. Further, linagliptin trough levels were numerically slightly higher in patients with continuous concomitant use of P-gp or CYP3A4 inhibitor (Visit 5: 8.89 mmol/L, Visit 7: 12.14 mmol/L) compared to patients not using any concomitant P-gp or CYP3A4 inhibitor (Visit 5: 6.36 mmol/L, Visit 7: 6.41 mmol/L), however the sample size of patients on concomitant P-gp inhibitors was low (up to 7 patients at Visit 7). At Week 12 and Week 24, the median DPP-4 inhibition at trough was greater than 80%. DPP 4 inhibition at trough increased with increasing linagliptin trough levels. Improvements in biomarkers for beta cell function were observed as an overall trend. Statistically significant and relevant differences between the 2 treatment groups were observed for proinsulin/insulin ratio (adjusted mean difference -0.039; SE 0.017; p = 0.0249), HOMA-%B (adjusted mean difference 22.21 (mU/L)/(mmol/L); SE 11.22; p = 0.0490), disposition index (adjusted mean difference 3.73 (1/((mmol/L)*(mmol/L)); SE 1.07; p = 0.0005), and total glucose AUC at 24 weeks (adjusted mean difference -3.26 mmol*h/L; p = 0.0026).
Safety results:	*Exposure*

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The mean exposure was 164 days for patients randomised to placebo and 169 days for patients randomised to linagliptin. The median exposure was 171 days in both groups with a range from 2 to 190 days in the placebo group and 1 to 207 days in the linagliptin group. A large majority of patients completed or nearly completed their planned exposure to the drug (>20 to 26 weeks): 89.8% of patients of the placebo group and 91.7% of patients of the linagliptin group. The duration of exposure was 155.0 patient years in the linagliptin group.

Adverse events

Overall, 98 patients (58.7%) were reported with AEs in the placebo group and 176 patients (52.4%) were reported with AEs in the linagliptin group. The majority of the AEs was of mild or moderate intensity. The most frequently reported AEs in both treatment groups were in the system organ classes (SOCs) infections and infestations (22.8% placebo; 16.4% linagliptin); metabolism and nutrition disorders (26.9% placebo; 13.1% linagliptin), musculoskeletal and connective tissue disorders (6.0% placebo; 9.5% linagliptin), and investigations (6.6% placebo; 6.3% linagliptin).

The SOCs in which AEs were reported with a numerically higher frequency in the linagliptin group than in the placebo group (with a frequency of at least 2% in either treatment group on the preferred term level) were blood and lymphatic system disorders (1.2% placebo; 2.1% linagliptin); nervous system disorders (2.4% placebo; 4.5% linagliptin); eye disorders (1.2% placebo; 2.1% linagliptin); cardiac disorders (0.6% placebo; 3.6% linagliptin); vascular disorders (1.2% placebo; 5.1% linagliptin); respiratory, thoracic and mediastinal disorders (1.2% placebo; 3.9% linagliptin); skin and subcutaneous tissue disorders (1.8% placebo; 4.5% linagliptin); and musculoskeletal and connective tissue disorders (6.0% placebo; 9.5% linagliptin). The most frequently (at least 2%) reported AEs by preferred term and with a numerically higher frequency in the linagliptin group than in the placebo group were: headache (1.2% placebo; 2.7% linagliptin), hypertension (1.2% placebo; 3.6% linagliptin), and back pain (1.8% placebo; 2.7% linagliptin). The following AEs by preferred term, which occurred with an numerically higher frequency in the linagliptin group, had an incidence rate of less than 2% but are commonly observed with DPP-4 inhibitors or are of interest in the development of new antidiabetic drugs: hypertensive crisis (0.6%) and single cases of aortic arteriosclerosis, hypotension, temporal arteritis, and thrombophlebitis in the SOC vascular

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disorders; and eosinophilia (0.9%), anaemia (0.6%), leukopenia (0.6%), neutropenia (0.3%) within the SOC blood and lymphatic system disorders. In the SOC cardiac disorders, angina pectoris (0.6%), coronary artery disease (0.6%), supraventricular extrasystoles (0.6%), and single cases of atrial fibrillation, atrioventricular block first degree, left bundle branch block, extrasystoles, myocardial ischaemia, sinus arrhythmia, sinus bradycardia, and ventricular extrasystoles were reported. Within the SOC skin and subcutaneous tissue disorders, pruritus (0.9%), eczema (0.6%), hyperhidrosis (0.6%), skin ulcer (0.6%) and single cases of dermatitis, alopecia areata, allergic dermatitis, contact dermatitis, exfoliative dermatitis, skin lesion, and swelling face were reported. Note, that there was an imbalance in vascular disorders, cardiac disorders, and skin and subcutaneous tissue disorders at baseline with numerically higher incidences in the linagliptin group than in the placebo group.

In the linagliptin group, 5.1% of patients were reported with drug-related AEs, in the placebo group 3.6% of patients. The most frequent PT was hyperglycaemia reported by 2 patients (1.2%) in the placebo group and 3 patients (0.9%) in the linagliptin group. In the linagliptin group, there were 2 cases of skin disorders (1 patient reported with eczema and another patient with pruritus). Within the SOC investigations, there were 3 cases in the linagliptin group: 1 patient was reported with increased aspartate transaminase (AST) and increased alanine transaminase (ALT), 1 patient with increased blood amylase, and 1 patient with decreased platelet count. Four patients in each treatment group (2.4% placebo and 1.2% linagliptin) were reported with AEs leading to discontinuation. All of these events except two (erectile dysfunction reported by one patient in the placebo group and cough reported by one patient in the linagliptin group) were assessed as not related to the study medication. There were 2 patients with a hypoglycaemic adverse event as defined by the investigator, one in each treatment group (0.6% placebo and 0.3% linagliptin). The patient treated with placebo was reported with hypoglycaemia and had 1 hypoglycaemic episode while he was on rescue medication. The patient treated with linagliptin was reported with asthenia and had 2 to 3 hypoglycaemic episodes and was not on rescue medication. In both cases, no assistance was required. During the trial, 10 patients were reported with cardiac and cerebrovascular events that qualified for adjudication. Out of these, 2 events were confirmed by the adjudication committee: 2 patients (62309 and 62765) in the linagliptin group were reported with stable angina.

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There were no fatal cases in this study. Overall, the number of patients with serious adverse events (SAEs) was low: 7 patients (4.2%) in the placebo group and 10 patients (3.0%) in the linagliptin group. None of the events was assessed as related to the study medication. In the placebo group, 2 patients were reported with breast cancer, 1 patient with inadequate control of diabetes mellitus, 1 patient with atrial fibrillation and coronary artery disease, 1 patient with decreased platelet count, 1 patient with foot fracture, and 1 patient with road traffic accident and rib fracture. In the linagliptin group, there were single cases of pharyngeal cellulitis, pneumonia, atrial fibrillation, coronary artery disease, hypertensive crisis, hypotension, temporal arteritis, and back pain; 1 patient was reported with intervertebral disc protrusion and Non-Hodgkin's lymphoma, another patient was reported with road traffic accident and hand fracture.

Significant AEs (i.e. protocol-defined) were analysed based on standardised MedDRA query (SMQ). In the placebo group, 1 patient was reported with increased ALT and increased AST and 1 patient with increased hepatic enzymes. In the linagliptin group, 1 patient was reported with hypotension. Other significant AEs (as defined by ICH E3) were reported for 2 patients in each treatment group (1.2% placebo and 0.6% linagliptin). In the placebo group, 1 patient was reported with haematuria and 1 patient with erectile dysfunction. In the linagliptin group, 1 patient was reported with cough and 1 patient with musculoskeletal chest pain.

Laboratory evaluation and vital signs

Laboratory analyses (haematology, clinical chemistry, and urinalysis) and vital signs (blood pressure and pulse rate) did not reveal any clinically significant findings. Few patients were reported with possibly clinically significant abnormalities. There were no cases of Hy's law in this study. Regarding changes in renal function, no notable difference between treatments was observed.

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Conclusions:	In conclusion, a clinically relevant reduction in HbA_{1c} change from baseline to Week 24 was observed for linagliptin compared to placebo. Superiority of linagliptin over placebo in HbA_{1c} reduction was shown and treatment with linagliptin was well tolerated. The reported safety results were comparable between linagliptin and placebo. The incidence of hypoglycaemic events during treatment with linagliptin was very low. In this study, linagliptin was efficacious and well tolerated and no safety concerns arose.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and/or results for primary and secondary endpoints of the trial.

Results for	presented in
HbA1c (%) change from baseline over time	Table 15.2.1.2.1: 5

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)	8.00 (0.07)	8.00 (0.05)		
Week 6	0.10 (0.05)	-0.37 (0.04)	-0.47 (-0.601,-0.348)	<0.0001
Week 12	0.17 (0.07)	-0.47 (0.05)	-0.64 (-0.796,-0.477)	<0.0001
Week 18	0.22 (0.08)	-0.47 (0.05)	-0.68 (-0.863,-0.504)	<0.0001
Week 24	0.26 (0.08)	-0.45 (0.05)	-0.71 (-0.888,-0.533)	<0.0001

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

Source: Appendix 16.1.9.2 Statdoc 6.1.2.1.4