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: Not applicable		**EudraCT No.:** 2007-002450-28	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 DEC 2009	**Trial No. / U No.:** 1218.18 / U09-2458-02	**Date of trial:** 25 FEB 2008 – 21 MAY 2009	**Date of revision:** 19 FEB 2010

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 type 2 diabetic patients with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial: 100 trial centres in 11 countries (Argentina, Belgium, Canada, China, Germany, Korea, Philippines, Russia, Taiwan, Turkey, and the United Kingdom)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this study was to investigate the efficacy and safety of linagliptin 5 mg versus placebo administered for 24 weeks as add-on to a background therapy of metformin in combination with sulphonylurea (SU) to patients with type 2 diabetes mellitus and insufficient glycaemic control.
Methodology:	Randomised, placebo-controlled, double-blind, parallel-group comparison of linagliptin versus placebo over 24 weeks. Before randomisation, patients underwent a 2-week placebo run-in period.
No. of patients:	
planned:	Entered: 800
actual:	Enrolled: 1598
	Linagliptin 5 mg Entered: 793 treated: 792 analysed (for primary endpoint): 778
	Placebo Entered: 265 treated: 263 analysed (for primary endpoint): 262

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Diagnosis and main criteria for inclusion:	Patients ≥18 and ≤80 years, BMI ≤40 kg/m^2, diagnosed with type 2 diabetes mellitus and with insufficient glycaemic control despite therapy with the combination of metformin and SU; glycosylated haemoglobin [HbA_{1c}] ≥7.0% and ≤ 10.0%.
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.:	B071002355 and B071003943
Duration of treatment:	2-week placebo run-in period followed by 24-week treatment period and 1-week follow-up period. Background medication (metformin in combination with SU) was to be taken during the entire trial duration (including the screening and placebo run-in periods) in an unchanged dosage.
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, and clinical laboratory parameters

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Statistical methods:

Primary endpoint: Testing of superiority hypothesis versus placebo using analysis of covariance (ANCOVA) with treatment as factor and baseline HbA_{1c} as covariate

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 1598 patients were enrolled; 1136 patients entered the 2-week placebo run-in period; 1058 were randomised in a 1:3 ratio to receive treatment with either placebo (265 patients) or linagliptin 5 mg (793 patients). Three of the randomised patients were not treated, and therefore 1055 patients were treated with either placebo (263 patients) or linagliptin (792 patients). Of the treated patients, 976 patients (92.5%) did not prematurely discontinue trial medication; 79 patients (7.5%) prematurely discontinued trial medication (8.0% placebo; 7.3% linagliptin) most frequently due to AEs.

Overall, the demographic data were well balanced between the treatment groups. The majority of the treated population comprised either Asians (51.7%) or Whites (46.6%); 52.8% were females, mean age of patients were 58.1 years and mean BMI was 28.3 kg/m^2. The mean baseline HbA_{1c} (standard deviation SD) was 8.14% (0.84) in the placebo group and 8.15% (0.80) in the linagliptin groups. The mean baseline FPG (SD) was 162.6 mg/dL (37.1) in the placebo group and 159.3 mg/dL (36.5) in the linagliptin group. The renal function estimated as the glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) formula. At baseline, normal renal function, i.e., eGFR ≥90 mL/min was reported for 57.0% of the patients (60.1% placebo; 55.9% linagliptin); 34.6% of the patients had mild renal impairment (60 to <90 mL/min; 31.6% placebo; 35.6% linagliptin), 5.0% of the patients had moderate renal impairment (30 to <60 mL/min; 6.1% placebo; 4.7% linagliptin). No patients were reported with severe renal impairment (<30 mL/min).

Primary endpoint

The primary endpoint of adjusted mean change in HbA_{1c} from baseline at Week 24 was analysed in the full analysis set (FAS), i.e., all patients who had a

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baseline and at least one on-treatment HbA_{1c} measurement available. Superiority of linagliptin (778 patients) over placebo (262 patients) was demonstrated for the primary endpoint (mean treatment difference: −0.62%, standard error [SE]: 0.06, 95% CI: −0.73, −0.50, p<0.0001).

All sensitivity analyses reconfirmed the superiority of linagliptin over placebo. The difference between treatments in terms of adjusted mean change from baseline in HbA_{1c} (SE) steadily increased over time, across visits (from −0.49% [0.04] at Week 6 to −0.62% [0.06] at Week 24, p<0.0001). In the linagliptin treatment group, the maximum adjusted mean reduction in HbA_{1c} (SE) was observed at Week 12 (−0.84% [0.03]). A near significant interaction with treatment at the 10% level was observed for the subgroups baseline HbA_{1c} (p=0.0728, lower baseline leads to a smaller treatment difference), country (p=0.0840, slightly greater treatment differences in some countries), HOMA−IR (p=0.0529), and HOMA−%B (p=0.0856, no clear trends in both).

Secondary endpoints

The adjusted mean difference between linagliptin and placebo for the change in FPG from baseline at Week 24 was −12.7 mg/dL (SE: 2.8%, p<0.0001). All sensitivity analyses were consistent with the results for the FAS.

Concerning the treat-to-target efficacy response, among patients with baseline HbA_{1c} ≥7.0%, 8.1% of the patients in the placebo group and 29.2% of the patients in the linagliptin group achieved HbA_{1c} <7.0%. The odds of achieving HbA_{1c} levels <7.0% were 5.5−times higher with linagliptin treatment than with placebo treatment (odds ratio: 5.510, p<0.0001). Among patients with baseline HbA_{1c} ≥6.5%, 4.2% of the patients in the placebo group and 13.1% of the patients in the linagliptin group achieved HbA_{1c} <6.5%. The odds of achieving HbA_{1c} levels <6.5% were 3.8-times higher with linagliptin treatment than with placebo treatment (odds ratio: 3.818, p<0.0001).

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%: 39.6% placebo; 66.9% linagliptin]; [8.0% to <9.0%: 32.6% placebo; 64.6% linagliptin]) than among patients with lower baseline HbA_{1c} ([7.0% to <8.0%: 25.0% placebo; 50.5% linagliptin]; [<7.0%: 20.0% placebo; 38.9% linagliptin]). The odds of achieving at least 0.5% HbA_{1c} reduction was 3.4-times higher with

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linagliptin treatment than with placebo (odds ratio: 3.360, p<0.0001).

Other endpoints

A higher proportion of patients in the placebo group (13.0%) received rescue medication than in the linagliptin group (5.4%). The odds of requiring rescue medication was about 3-times lower for patients treated with linagliptin as compared to placebo (odds ratio: 0.361, p<0.0001). No meaningful changes in mean weight or mean waist circumference were noted in both groups.

Biomarkers

A statistically significant and relevant treatment difference was observed for HOMA−%B (16.87 [mU/L]/[mmol/L], SE: 5.00, p=0.0008). The adjusted mean decreased from baseline to Week 24 in the placebo group (−9.07 [mU/L]/[mmol/L], SE: 4.34), whereas an increase was noted in the linagliptin group (7.81 [mU/L]/[mmol/L], SE: 2.47). Statistical significance was missed for DI (7.48 [1/mmol/L]*[mmol/L], SE: 4.07, p=0.0666). The adjusted mean change from baseline to Week 24 was −2.00 (1/mmol/L)*(mmol/L) [SE: 3.57] in the placebo group and 5.48 (1/mmol/L)*(mmol/L) [SE: 1.96] in the linagliptin group.

Safety results:

Exposure

The mean exposure of patients to either of the treatments was 166 days. Median exposure was 170 days for both groups. The majority of the patients in both groups (91.3% placebo; 93.2% linagliptin) completed the planned exposure time of >20 to 26 weeks. The overall duration of exposure to linagliptin was 358.9 patient years.

Adverse events (AE)

Overall, 157 patients, (59.7%) were reported with AEs in the placebo group and 525 patients, (66.3%) were reported with AEs in the linagliptin group. AEs of severe intensity were reported for few patients in both groups (1.5% placebo; 2.4% linagliptin), otherwise all AEs were mild or moderate in intensity. The most frequently reported system organ class (SOC) was 'metabolism and nutrition disorders' (25.9% placebo; 31.1% linagliptin). The SOCs reported at a numerically higher frequency in the linagliptin group than in the placebo group and with preferred terms (PT) reported at a frequency >2% in either treatment

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group were: metabolism and nutrition disorders (details above), followed by musculoskeletal and connective tissue disorders (9.1% placebo; 12.2% linagliptin), respiratory, thoracic and mediastinal disorders (2.7% placebo; 4.2% linagliptin), and vascular disorders (2.3% placebo; 4.3% linagliptin).

As skin disorders have been reported for other DPP-4 inhibitors, these are of particular interest. In this trial, AEs based on the SOC 'skin and subcutaneous tissue disorders' were reported at comparable frequencies in both groups (4.9% placebo; 4.9% linagliptin). The drug-related (linagliptin) AEs reported from this SOC were: hyperhidrosis (0.4%), rash (0.3%), pruritus, rash pruritic, skin exfoliation (all 0.1%). In the placebo group, hyperhidrosis (0.4%), rash (0.4%) and dermatitis allergic (0.4%) were reported drug-related. Since cardiovascular safety is of interest in the development of new antidiabetic drugs, AEs related to cardiac disorders were of specific interest. In the placebo group, 1.9% of the patients were reported with AEs in the SOC 'cardiac disorders' and in the linagliptin group, 2.5% of the patients reported AEs based on this SOC. None were assessed to be drug-related (linagliptin).

Drug-related AEs were reported by 11.4% of the patients in the placebo group and by 17.9% of the patients in the linagliptin group. The frequency of AEs leading to trial discontinuation was low (1.9% placebo; 2.9% linagliptin).

In this trial, hypoglycaemia (SOC: metabolism and nutrition disorders), was in general reported at a numerically higher frequency in the linagliptin group than in the placebo group as the most frequent PT for overall AEs, drug-related AEs, AEs leading to discontinuation, and 'other significant AEs '(ICH E3)'. For overall AEs, 14.8% of the patients in the placebo group were reported with hypoglycaemia as compared to 22.7% of the patients in the linagliptin group. Drug-related hypoglycaemia was reported in the placebo group (7.6%) at about half the frequency reported in the linagliptin group (14.5%). However hypoglycaemia leading to trial discontinuation was reported at a very low frequency (0.6% only in linagliptin).

Investigator-defined hypoglycaemia (i.e., protocol defined categories of hypoglycaemia and other PTs related to symptoms of hypoglycaemia) was reported by 16.0% of the patients in the placebo group and by 23.7% of the patients in the linagliptin group. Among these patients, severe hypoglycaemic episodes (i.e. those which required assistance of another person) were reported for 4.8% of the patients in the placebo group and by 2.7% of the patients in the

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linagliptin group. As expected due to the background therapy with SU and metformin, the logistic regression of the occurrence of any hypoglycaemic events indicated an odds ratio of 1.644 (p=0.0083), i.e., an increased probability of hypoglycaemic events with linagliptin treatment.

A total of 6 patients in the placebo group (2.3%) and 15 patients in the linagliptin group (1.9%) experienced events that qualified for adjudication by an independent external Clinical Event Committee (CEC). Out of these, 3 patients each in the placebo and in the linagliptin group were reported with CEC confirmed events. Confirmed incidences of 'other myocardial ischaemia' were comparable between placebo and linagliptin (0.8% placebo; 0.3% linagliptin); non-fatal myocardial infarction (0.1%) was reported only for the linagliptin group. Transient ischaemic attack (TIA) was seen only in the placebo group (0.4%).

There were no deaths reported during the conduct of this trial. The overall frequency of SAEs in this trial was low (3.8% placebo; 3.2% linagliptin). The most frequently reported PT was fall (0.4% placebo; 0.3% linagliptin). Only 1 SAE (renal impairment in 1 patient treated with linagliptin) was assessed to be drug-related. Note that this patient had moderate renal impairment (eGFR [MDRD]: 30 to <60 mL/min) at baseline.

The overall frequency of patients reported with protocol-defined significant AEs assessed via ‘standard MedDRA (medical drug dictionary for drug regulatory affairs) queries’ was low with hypersensitivity reactions being the most frequently reported (0.4% placebo; 1.4% linagliptin). 'Other significant AEs' (ICH E3 defined) were reported at a low frequency in this trial (1.9% placebo; 2.4% linagliptin).

Laboratory parameters and vital signs

Overall, mean values at baseline and at last value on treatment of almost all laboratory parameters were within reference ranges and the mean changes from baseline to last value on treatment were small. The observed shifts in laboratory values were not clinically significant. Overall, the frequencies of PCSAs reported were low and almost comparable between placebo and linagliptin groups. Increases in triglycerides were the most frequently reported PCSAs among all. Overall, PCSAs of clinical relevance were observed for haematological parameters, potassium, AST, ALT, CK and CK-MB. Note that

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	the changes in these laboratory parameters were also reported as AEs. Blood pressure and pulse rate remained almost unchanged during the course of this trial.
Conclusions:	In conclusion, linagliptin demonstrated efficacy by showing superiority to placebo in reducing HbA_{1c}, as add-on to a background therapy of metformin and sulphonylurea in patients with type 2 diabetes mellitus. Overall, fewer patients treated with linagliptin required rescue medication. The risk of hypoglycaemia was increased when linagliptin was added to a background therapy that included sulphonylurea. Overall, the treatment with linagliptin was well-tolerated and no other new safety concerns arose in this trial.

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**
HbA1c mean change from baseline over time	Table 15.2.1.2.2: 1
FPG mean change from baseline over time	Table 15.2.2.1: 6

Table 15.2.1.2.2: 1 Adjusted HbA1c (%) 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)	262	8.14	0.05	778	8.15	0.03					
Change from baseline at Week 6	262	-0.18	0.03	778	-0.67	0.02	-0.49	0.04	-0.56	-0.41	<.0001
Change from baseline at Week 12	262	-0.15	0.04	778	-0.84	0.03	-0.68	0.05	-0.78	-0.58	<.0001
Change from baseline at Week 18	262	-0.11	0.05	778	-0.81	0.03	-0.69	0.05	-0.80	-0.59	<.0001
Change from baseline at Week 24	262	-0.10	0.05	778	-0.72	0.03	-0.62	0.06	-0.73	-0.50	<.0001

* Model includes treatment and baseline HbA1c

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)	248	162.6	2.4	739	159.2	1.3					
Change from baseline at Week 6	248	6.3	2.0	739	-11.5	1.2	-17.8	2.3	-22.4	-13.2	<.0001
Change from baseline at Week 12	248	6.2	2.0	739	-9.5	1.2	-15.7	2.4	-20.3	-11.1	<.0001
Change from baseline at Week 18	248	7.4	2.2	739	-4.7	1.3	-12.1	2.6	-17.2	-7.1	<.0001
Change from baseline at Week 24	248	8.1	2.4	739	-4.6	1.4	-12.7	2.8	-18.1	-7.3	<.0001

* Model includes treatment, baseline HbA1c and baseline FPG