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: Trajenta®		**EudraCT No.:** 2009-015255-25	
Name of active ingredient: Linagliptin (BI 1356)		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 02 DEC 2011	**Trial No. / U No.:** 1218.63 / U11-1781-02	**Dates of trial:** 10 MAR 2010 – 22 JUN 2011	**Date of revision:** 02 FEB 2012

Title of trial:	A Phase III 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 (age ≥70 years) with insufficient glycaemic control (HbA_{1c} ≥7.0%) despite metformin and/or sulphonylurea and/or insulin therapy
Coordinating Investigator:	[redacted]
Trial sites:	Multi-national, multi-centre trial: 33 trial sites in 5 countries (Australia, Canada, Denmark, Netherlands, and Sweden)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	To investigate the efficacy and safety of linagliptin 5 mg once daily in elderly patients (≥70 years) with type 2 diabetes mellitus (T2DM) for 24 weeks.
Methodology:	Randomised, placebo-controlled, double-blind, parallel group comparison of 2 groups over 24 weeks, followed by a 1-week follow-up period. Patients who successfully completed the screening period underwent a 2-week open-label placebo run-in period before randomisation. Doses of background diabetes medications were kept stable during screening, run-in and the first 12 weeks of randomised treatment, after which adjustments were permitted.
No. of patients:	
planned:	Entered: 243
actual:	Enrolled: 377, randomised 241 Linagliptin 5 mg Randomised: 162 treated: 162 analysed (for primary endpoint): 160 Placebo Randomised: 79 treated: 79 analysed (for primary endpoint): 78

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Diagnosis and main criteria for inclusion:	Elderly patients with T2DM and insufficient glycaemic control (glycosylated haemoglobin, HbA_{1c} ≥7.0%) despite stable metformin and/or SU and/or insulin therapy; aged ≥70 years.
Test product:	Linagliptin, tablet
dose:	5 mg once daily
mode of admin.:	Oral
batch no.:	4000044
Reference therapy:	Placebo, tablet
dose:	Not applicable
mode of admin.:	Oral
batch no.:	4000048
Duration of treatment:	24 weeks followed by 1 week follow-up
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the HbA_{1c} change from baseline after 24 weeks of treatment. Important secondary endpoints were the change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment, occurrence of treat-to-target response (i.e. HbA_{1c} on treatment <7.0%), occurrence of relative efficacy response (i.e. HbA_{1c} lowering by 0.5%).
Safety:	Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory parameters.
Statistical methods:	Primary endpoint: Testing of superiority hypothesis of linagliptin 5 mg over placebo with an analysis of covariance (ANCOVA) with treatment and prior use of insulin as fixed classification effects and baseline HbA_{1c} as linear covariate. Secondary and other endpoints: ANCOVA (exploratory), descriptive statistics, for use of rescue medication logistic regression and Kaplan-Meier analysis. Safety endpoints: Descriptive statistics; for hypoglycaemic events logistic regression and Kaplan-Meier analysis.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Disposition and Compliance

All of the 241 patients who were randomised received trial medication. Of these, 21 patients (8.7%) prematurely discontinued trial medication (6.3% placebo; 9.9% linagliptin). More than 97% of patients were compliant up to Week 24.

Demographics

Overall, the demographic profile was balanced between the treatment groups. However, there were more male patients in the linagliptin group (71.6%) than in the placebo group (62.0%). Overall, there was a higher proportion of males enrolled in the trial (68.5%). Most patients were White (96.7%); patients of other races were Asian (2.1%) or Black or African American (1.2%). Mean age overall was 74.9 years; 44.4% of patients were 75 years of age or over. Background antidiabetes therapy with metformin was more common in the placebo group (88.5%) than in the linagliptin group (83.1%) whereas SU was more common in the linagliptin group (58.8%) than in the placebo group (55.1%). The proportions of patients with renal impairment were similar between the placebo and linagliptin 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/1.73m^2; 21.2%) or mild renal impairment (eGFR 60 to <90 mL/min/1.73m^2; 51.9%). The total percentage of patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73m^2) was 25.7%. Only 1.2% of patients had severe renal impairment (eGFR <30 mL/min/1.73m^2).

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Efficacy / clinical pharmacology results: (continued)

Primary endpoint

The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The primary efficacy analysis was based on the full analysis set (FAS), which included all treated patients with a baseline and at least one on-treatment HbA_{1c} measurement available. The estimated treatment difference between linagliptin (n=160) and placebo (n=78), calculated as the adjusted mean change from baseline in HbA_{1c} at Week 24, was -0.64% (95% confidence interval, CI -0.81, -0.48; $p<0.0001$), demonstrating superiority of linagliptin over placebo in the reduction of HbA_{1c}. Sensitivity analyses on the per protocol set (PPS) last observation carried forward (LOCF) analysis set confirmed these results.

Secondary endpoints

The differences in treatment groups in adjusted mean changes from baseline were -0.35% at Week 6 and -0.57% at Week 12. The difference between the treatment groups in mean changes in HbA_{1c} was sustained beyond 12 weeks, even though dose adjustment in background therapy was allowed after this time.

The differences between the placebo and linagliptin groups in adjusted mean change from baseline in HbA_{1c} was statistically significant ($p<0.0001$) both for patients aged <75 years and for patients aged ≥75 years. Similarly there was a statistically significant difference between the effects of linagliptin and placebo ($p<0.0001$) in patients diagnosed with T2DM more than 10 years before enrolment in the study.

There was a statistically significant difference between the linagliptin and placebo group in reduction in FPG. The estimated difference in the adjusted mean change from baseline to Week 24 in FPG between linagliptin and placebo was -20.7 mg/dL ($p<0.0001$). The difference between the groups was sustained up to 24 weeks, even though changes in background therapy were permitted after Week 12 ($p\leq0.0001$). Sensitivity analyses confirmed the observed results.

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Efficacy / clinical pharmacology results: (continued)

Significantly more patients on linagliptin with baseline HbA_{1c} ≥7.0% achieved the target treatment outcome of HbA_{1c} <7.0% after 24 weeks of treatment (8.3% placebo; 38.9% linagliptin; p<0.0001). The proportion of patients with an HbA_{1c} reduction of at least 0.5% at Week 24 was 12.8% of patients on placebo and 54.4% of patients on linagliptin.

Other endpoints

Overall, use of rescue medication was not high. However, the proportion of patients requiring rescue therapy was greater for the placebo group compared with the linagliptin group (14.1% placebo; 4.4% linagliptin). The odds ratio of requiring rescue therapy overall was 0.214 (95% CI: 0.073, 0.625; p = 0.0048). Similarly, changes in background antidiabetes therapy were uncommon, although a higher proportion of patients in the placebo group (13.5%) had at least one change in background antidiabetes therapy between Week 12 and Week 24 compared with patients in the linagliptin group (5.8%).

There was no effect of linagliptin on body weight, with no clinically relevant difference between the groups in change from baseline to Week 24 (-0.6 kg placebo; -0.2 kg linagliptin).

Pharmacokinetic/pharmacodynamic results

The overall geometric mean trough plasma concentration of linagliptin was 6.494 nmol/L (n=36). Plasma concentration of linagliptin after 24 weeks of treatment categorised by eGFR showed similar mean plasma trough linagliptin levels with worsening renal function. The differences were not statistically significant and are not considered clinically relevant.

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Safety results:

Exposure

All 241 randomised patients received at least one dose of study medication and were included in the Treated Set: 79 patients received placebo and 162 patients received linagliptin. Mean exposure to study medication was 163.8 days for patients randomised to placebo and 159.7 days for patients randomised to linagliptin. Cumulative patient exposure in the linagliptin group was 70.9 patient years.

Adverse events

Overall, 60 patients (75.9%) were reported with AEs in the placebo group and 123 patients (75.9%) were reported with AEs in the linagliptin group. The majority of the AEs were of mild or moderate intensity. The most frequently reported AEs across both treatment groups were in the system organ classes (SOCs) infections and infestations (35.4% placebo; 29.6% linagliptin), followed by metabolism and nutrition disorders (24.1% placebo; 26.5% linagliptin), gastrointestinal disorders (16.5% placebo; 13.6% linagliptin), nervous system disorders (15.2% placebo; 9.9% linagliptin), and musculoskeletal and connective tissue disorders (10.1% placebo; 14.8% linagliptin). The most commonly reported AEs on preferred term (PT) level were hypoglycaemia (16.5% placebo; 22.8% linagliptin), followed by nasopharyngitis (8.9% placebo; 10.5% linagliptin), hyperglycaemia (10.1% placebo; 5.6% linagliptin), urinary tract infection (6.3% placebo; 4.3% linagliptin), and upper respiratory tract infection (6.3% placebo; 3.7% linagliptin).

AEs that were assessed by the investigators as being drug-related were reported in 13.9% of patients in the placebo group and 21.0% of patients in the linagliptin group. The most common PTs of drug-related AEs were hypoglycaemia (8.9% placebo; 14.2% linagliptin group), followed by diarrhoea (0.0% placebo; 1.2% linagliptin) and dry mouth (2.5% placebo; 0.0% linagliptin). All other drug-related AEs occurred in only one patient each.

AEs led to discontinuation of study medication in 1.3% of patients in the placebo group and 4.9% of patients in the linagliptin group. Two of the AEs that led to discontinuation of study medication were considered drug-related: depressed mood (placebo group), and insomnia (linagliptin group). The remaining AEs that led to discontinuation of study medication were all isolated cases in patients in the linagliptin group and all were considered not to be drug-related.

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Safety results: (continued)

There were 13 patients (16.5%) in the placebo group and 39 patients (24.1%) in the linagliptin group with an investigator-defined hypoglycaemic episode. Of the patients with hypoglycaemia, asymptomatic hypoglycaemia was reported with a higher incidence in the placebo group than in the linagliptin group (38.5% placebo; 25.6% linagliptin), as was symptomatic (moderate) hypoglycaemia with plasma glucose <54 mg/dL (38.5% placebo; 28.2% linagliptin), whereas symptomatic (mild) hypoglycaemia with plasma glucose ≥54 to ≤70 mg/dL more common in the linagliptin group than in the placebo group (38.5% patients with hypoglycaemia on placebo; 71.8% patients with hypoglycaemia on linagliptin). One patient in the linagliptin group (on background antidiabetes medication of metformin and SU) had a severe episode of hypoglycaemia. The proportion of patients reported with investigator-defined hypoglycaemia by age group was similar for the two treatment groups in patients younger than 75 years of age (23.3% placebo; 25.3% linagliptin), but was low in the placebo group in patients aged 75 years or older (8.3% placebo; 22.5% linagliptin). No patients aged >75 years had severe hypoglycaemia. Logistic regression of the occurrence of hypoglycaemia indicated that treatment group was not associated with a significant difference in the odds of having a hypoglycaemic event (odds ratio 1.577, p = 0.2083). Age was not a significant factor (odds ratio 1.490, p = 0.2414), whereas background antidiabetes medication (particularly SU and insulin) was significant (p = 0.0005). The odds ratios for metformin:SU with or without metformin was 0.090 and for metformin:insulin was 0.049.

Two patients, both in the linagliptin group, had confirmed cardiac or cerebrovascular events adjudicated by the Clinical Endpoint Committee. One patient had a non-fatal ischaemic stroke and another patient was hospitalised due to coronary artery disease (unstable angina).

There were no fatal cases in this study. There were 5 patients (6.3%) in the placebo group and 14 patients (8.6%) in the linagliptin group who were reported with SAEs during the treatment period. None of the SAEs were considered related to trial medication. In the linagliptin treatment group, SAEs were reported in the SOCs cardiac disorders (4 patients), gastrointestinal disorders (1 patient), infections and infestations (4 patients), injury, poisoning and procedural complications (3 patients), metabolism and nutrition disorders (1 patient), and nervous system disorders (2 patients).

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Safety results: (continued)

In the placebo group, SAEs were reported in the SOCs infections and infestations (1 patient), neoplasms benign, malignant and unspecified (including cysts and polyps) (3 patients), and renal and urinary disorders (1 patient).

The analysis of significant AEs (i.e. protocol-defined) was based on Standardised MedDRA (Medical Dictionary for Regulatory Activities) Queries. Three patients, all in the linagliptin group, had a total of 4 significant AEs: contact dermatitis, eczema, acute renal failure, and increased blood creatinine. No patients in the study had pancreatitis. Other significant AEs (as defined by ICH E3), i.e. non-serious AEs that led to discontinuation of study medication, were reported by 1 patient (1.3%) in the placebo group (depressed mood) and 4 patients (2.5%) in the linagliptin group (urine analysis abnormal, dizziness, Parkinson's disease, and insomnia).

Laboratory evaluation and vital signs

Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically significant findings compared to baseline. Few patients were reported with possibly clinically significant abnormalities. There were no cases of Hy's law in this study. No notable differences in changes in renal function were observed between treatments.

Overall, no clinically significant differences between the treatment groups were observed in blood pressure and pulse rate from baseline to end of treatment.

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Conclusions:

In a population of elderly patients with insufficient glycaemic control despite treatment with other antidiabetes medications, treatment with 5 mg linagliptin once daily was superior to placebo in the reduction of HbA_{1c} and FPG levels. The difference in the adjusted means of -0.64% HbA_{1c} lowering between linagliptin and placebo treatment is clinically relevant. Linagliptin was shown to be efficacious for patients with diabetes durations of greater than 10 years. Trough levels of linagliptin were in line with previous trials and between patients with normal renal function and patients with mild to moderate renal impairment. Linagliptin was weight neutral and the assessment of safety did not reveal any major concerns for treatment with linagliptin in the elderly population. The incidence of hypoglycaemia was similar in both groups and in line with previous studies in patients taking the same background antidiabetes medications. Mild hypoglycaemia was reported in a higher proportion of patients on linagliptin than placebo but the difference between the groups was attributed to background SU. For elderly patients, linagliptin was efficacious and well tolerated and no safety concerns were raised.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for 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**
HbA_{1c} (%) change from baseline over time	Table 15.2.1.2.2: 2
FPG (mg/dL) change from baseline over time	Table 15.2.2.1: 4

Table 15.2.1.2.2: 2 Adjusted HbA1c (%) mean change from baseline over time - FAS (LOCF)

Time point number = Baseline

	Placebo	Lina 5 mg qd
Number of patients in analysis set	78	160
Baseline Mean (SE)	7.70 (0.08)	7.82 (0.06)

* Model includes treatment, continuous baseline HbA1c and prior use of insulin.

Table 15.2.1.2.2: 2 Adjusted HbA1c (%) mean change from baseline over time - FAS (LOCF)

Time point number = Week 6

	Placebo	Lina 5 mg qd
Number of patients in analysis set	78	160
Number of patients analysed	78	160
Week 6		
Mean (SE)	7.61 (0.07)	7.36 (0.06)
Change from baseline		
Mean (SE)	-0.09 (0.04)	-0.46 (0.03)
Adjusted* mean (SE)	-0.07 (0.05)	-0.42 (0.03)
Comparison vs. Placebo (diff. Linagliptin - Placebo)		
Adjusted* mean (SE)		-0.35 (0.05)
95% Confidence interval		(-0.45, -0.24)
p-value		<.0001

* Model includes treatment, continuous baseline HbA1c and prior use of insulin.

Table 15.2.1.2.2: 2 Adjusted HbA1c (%) mean change from baseline over time - FAS (LOCF)

Time point number = Week 12

	Placebo	Lina 5 mg qd
Number of patients in analysis set	78	160
Number of patients analysed	78	160
Week 12		
Mean (SE)	7.64 (0.08)	7.15 (0.06)
Change from baseline		
Mean (SE)	-0.06 (0.06)	-0.67 (0.05)
Adjusted* mean (SE)	-0.03 (0.06)	-0.60 (0.05)
Comparison vs. Placebo (diff. Linagliptin - Placebo)		
Adjusted* mean (SE)		-0.57 (0.07)
95% Confidence interval		(-0.71, -0.43)
p-value		<.0001

* Model includes treatment, continuous baseline HbA1c and prior use of insulin.

Table 15.2.1.2.2: 2 Adjusted HbA1c (%) mean change from baseline over time - FAS (LOCF)

Time point number = Week 18

	Placebo	Lina 5 mg qd
Number of patients in analysis set	78	160
Number of patients analysed	78	160
Week 18		
Mean (SE)	7.70 (0.08)	7.16 (0.06)
Change from baseline		
Mean (SE)	-0.00 (0.07)	-0.66 (0.05)
Adjusted* mean (SE)	0.04 (0.07)	-0.58 (0.05)
Comparison vs. Placebo (diff. Linagliptin - Placebo)		
Adjusted* mean (SE)		-0.62 (0.08)
95% Confidence interval		(-0.77, -0.47)
p-value		<.0001

* Model includes treatment, continuous baseline HbA1c and prior use of insulin.

Table 15.2.1.2.2: 2 Adjusted HbA1c (%) mean change from baseline over time - FAS (LOCF)

Time point number = Week 24

	Placebo	Lina 5 mg qd
Number of patients in analysis set	78	160
Number of patients analysed	78	160
Week 24		
Mean (SE)	7.72 (0.09)	7.15 (0.06)
Change from baseline		
Mean (SE)	0.02 (0.08)	-0.67 (0.05)
Adjusted* mean (SE)	0.04 (0.07)	-0.61 (0.06)
Comparison vs. Placebo (diff. Linagliptin - Placebo)		
Adjusted* mean (SE)		-0.64 (0.08)
95% Confidence interval		(-0.81, -0.48)
p-value		<.0001

* Model includes treatment, continuous baseline HbA1c and prior use of insulin.

Table 15.2.2.1: 4 Adjusted means for FPG (mg/dL) change from baseline over time analysis - FAS (OC)

	Placebo	Lina 5 mg qd
Baseline		
Unadjusted mean (SE)	144.1 (3.3)	152.7 (2.3)
Week 6		
Adjusted mean (SE)	4.6 (2.7)	-14.1 (2.0)
Difference: Linagliptin - Placebo		
Adjusted mean (SE)		-18.6 (3.1)
95% CI		(-24.7,-12.6)
p-value		<.0001
Week 12		
Adjusted mean (SE)	6.8 (2.9)	-14.7 (2.1)
Difference: Linagliptin - Placebo		
Adjusted mean (SE)		-21.5 (3.4)
95% CI		(-28.1,-14.8)
p-value		<.0001
Week 18		
Adjusted mean (SE)	9.6 (3.6)	-12.0 (2.5)
Difference: Linagliptin - Placebo		
Adjusted mean (SE)		-21.6 (4.2)
95% CI		(-29.8,-13.4)
p-value		<.0001
Week 24		
Adjusted mean (SE)	9.4 (4.4)	-11.3 (3.1)
Difference: Linagliptin - Placebo		
Adjusted mean (SE)		-20.7 (5.2)
95% CI		(-31.0,-10.4)
p-value		0.0001

Mixed model includes treatment, continuous baseline HbA1c, continuous baseline fasting plasma glucose, prior use of insulin, week repeated within patient, week by treatment interaction.