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.:** 2007-002456-41	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 10	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 JAN 2010	**Trial No. / U No.:** 1218.15/ U09-2519-01	**Dates of trial:** 15 APR 2008 – 19 JUN 2009	**Date of revision** (if applicable): Not applicable

Title of trial:	A randomised, double-blind, placebo controlled, parallel group, 24-week study to assess the efficacy and safety of linagliptin (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug-naïve or previously treated type 2 diabetic patients with insufficient glycaemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial: 43 trial sites in 7 countries (Austria, Greece, Hungary, Japan, Portugal, Romania, and Spain)
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 once daily) versus placebo administered for 24 weeks as initial combination with pioglitazone 30 mg in 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 any 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: 375
actual:	Enrolled: 707 Linagliptin 5 mg Entered: 259 treated: 259 analysed (for primary endpoint): 252 Placebo Entered: 130 treated: 130 analysed (for primary endpoint): 128

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Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus and insufficient glycaemic control (7.5%≤ HbA_{1c} ≤11.0% at randomization); 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, B071003944
Test product:	Pioglitazone
dose:	30 mg once daily
mode of admin.:	Overencapsulated tablets
batch no.:	B071002479, B081001791
Reference therapy:	Placebo for linagliptin
dose:	Not applicable
mode of admin.:	Tablet, oral
batch no.:	B071002355, B071003943
Reference therapy:	Placebo for pioglitazone (administered during run-in period)
dose:	Not applicable
mode of admin.:	Capsule, oral
batch no.:	B071002353
Duration of treatment:	Six-week washout period including placebo run-in during the last 2 weeks (patients pre-treated with an 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%).
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 safety endpoints: descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

In this study, 707 patients were enrolled in 43 centres in Europe and Asia. A total of 389 patients were randomised in a 1:2 ratio to receive (once daily) either placebo plus pioglitazone 30 mg (pbo+pio), or linagliptin 5 mg plus pioglitazone 30 mg (lina+pio). About 45% (318 patients) of the enrolled patients were not randomised, mainly due to failure to meet the inclusion criteria regarding the range of HbA_{1c} levels. A total of 389 patients were treated (130 patients pbo+pio; 259 patients lina+pio) with randomised study medication. Of those, 34 patients (8.7%) prematurely discontinued trial medication (14.6% pbo+pio; 5.8% lina+pio).

The demographic baseline characteristics were comparable between the treatment groups. Overall, the mean age was 57.5 years; 74.6% of patients were white, 24.9% were Asian; 60.9% of patients were male. The mean baseline weight was 82.7 kg in the pbo+pio group and 78.3 kg in the lina+pio group. Mean baseline body mass index was 29.7 kg/m^2 in the pbo+pio group, and 28.7 kg/m^2 in the lina+pio group. At baseline, 52.4% of patients had normal renal function (eGFR $\geq$ 90 mL/min), 39.1% had mild renal impairment (eGFR 60 to 89 mL/min), and 4.4% had moderate renal impairment (eGFR 30 to 59 mL/min).

Baseline HbA_{1c} was comparable between both treatment groups with a mean of 8.59% (SD 0.82), with 8.58% (SD 0.87) for pbo+pio and 8.60% (SD 0.79) for lina+pio. Mean baseline FPG was 189.9 mg/dL (SD 43.0), with 190.3 mg/dL (SD 43.8) for pbo+pio and 189.8 mg/dL (SD 42.7) for lina+pio. Nearly half of the patients (49.7%) had not received antidiabetic medication previously, 31.8% had been receiving 1 oral antidiabetic drug (OAD), and 18.4% had been receiving more than 1 OAD. Percentages of patients in each of the prior oral antidiabetic groups were similar for both treatment groups.

The primary analysis of the efficacy endpoints was performed on the full analysis set (FAS) of patients (n=380) which comprised all patients who had a

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baseline and at least one on-treatment HbA_{1c} measurement available (pbo+pio: 128 patients; lina+pio 252 patients). The last observation carried forward (LOCF) approach was applied.

Primary endpoint

Superiority of linagliptin + pioglitazone over placebo + pioglitazone was demonstrated by the primary analysis of the primary endpoint of change in HbA_{1c} from baseline after 24 weeks of treatment. Patients in both treatment groups showed a reduction in HbA_{1c} after 24 weeks of treatment. The adjusted mean HbA_{1c} change from baseline for the lina+pio group was −1.06% (SE 0.06), compared with −0.56% (SE 0.09) observed in the pbo+pio group. The difference in the adjusted mean of lina+pio compared with pbo+pio was −0.51% (95% CI: −0.71, −0.30; $p<0.0001$).

Sensitivity analyses confirmed the superiority of lina+pio shown in the primary analysis. An analysis of covariance (ANCOVA) model applied to assess the treatment effect on the primary endpoint across the range of baseline HbA_{1c} values and the number of prior OADs showed a statistically significant interaction ($p=0.0145$), where patients previously treated with monotherapy displayed a larger treatment difference than treatment-naïve patients. No treatment difference was noted in patients previously treated with combination therapy.

As additional sensitivity analysis, a mixed model for repeated measurement analysis showed that both treatment regimens produced a reduction in HbA_{1c} over time that was larger in the lina+pio group than in the pbo+pio group ($p<0.0001$ at each visit). The difference between treatments in terms of adjusted mean change from baseline in $HbA_{1c,}$ increased over time during the first 12 weeks (difference between treatments of −0.50%) and then remained constant to week 24 (−0.51%).

Subgroup analyses of HbA_{1c} showed significant treatment-by-subgroup interaction terms ($p <0.1$) in prior OADs, region, race, gender and HOMA-%B (homeostatic model assessment of β-cell function / insulin secretion). The subgroup analysis for prior OADs confirmed the results from the ANCOVA model including treatment group by prior OADs interaction term described above ($p=0.0266$). A significant interaction was observed for the subgroup 'region' due to the treatment difference observed between Asian and European

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patients on treatment with pbo+pio, where Asian patients had a change from baseline of −0.05% compared with −0.71% in European patients (p=0.0238). This was also reflected in the significance of the 'race' subgroup interaction (p=0.0774). In the pbo+pio group, female patients (−0.93%) displayed a much larger change from baseline in HbA_{1c} than male patients (−0.34%), with a p-value of 0.0856. Finally, for HOMA-%B, the subgroup analysis results suggested that the lower the baseline category (i.e. the worse the β-cell function was at baseline), the greater the treatment difference after 24 weeks (p=0.0871).

Secondary endpoints

The results for FPG were in line with those observed for HbA_{1c}. Treatment with lina+pio resulted in a larger adjusted mean change from baseline than treatment with pbo+pio, with a treatment difference at 24 weeks of −14.2 mg/dL (95% CI −21.1, −7.3; p<0.0001). Sensitivity analyses confirmed these results. As with HbA_{1c}, larger treatment differences were observed for patients that had received 1 prior OAD compared with treatment-naïve patients, while the smallest difference was observed in patients that had previously received a combination of antidiabetic agents. Similarly, when analysed over time, FPG values in the lina+pio group exhibited greater reductions in the first 12 weeks of randomised treatment than in the pbo+pio group (p<0.0001 at each visit). The difference between treatment groups in the adjusted mean change from baseline was −13.2 mg/dL at week 12, and −14.2 mg/dL at week 24.

An analysis of absolute response (target HbA_{1c} of 7.0% and 6.5 %,) and relative efficacy response (HbA_{1c} reduction of at least 0.5%) after 24 weeks of treatment, was carried out. Results indicated that patients with HbA_{1c} values ≥7.0% at baseline on treatment with lina+pio were more likely to achieve the <7.0% HbA_{1c} category than patients on treatment with pbo+pio (30.5% of patients pbo+pio; 42.9% of patients lina+pio), with an associated odds ratio of 2.10 (p=0.0051). The target of HbA_{1c}<6.5%, was observed in 14.1% of patients on treatment with pbo+pio and 17.5% of patients on treatment with lina+pio (odds ratio: 1.35; p=0.3547). Patients treated with lina+pio were also more likely to have an HbA_{1c} reduction of at least 0.5% after 24 weeks of treatment than patients treated with pbo+pio (50.8% patients pbo+pio; 75.0% of patients lina+pio), with an associated odds ratio of 3.82 (p<0.0001).

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	Other endpoints During the trial, 14.1% of patients on treatment with pbo+pio and 7.9% of patients on treatment with lina+pio received rescue therapy. The associated odds ratio of 0.446 (p=0.0352) indicated that patients on treatment with pbo+pio were more likely to require rescue medication. In general, patient weight increased during the study (a known class effect of thiazolidinediones), with an adjusted mean of the change from baseline of 2.3 kg in the lina+pio group and of 1.2 kg in the pbo+pio group. This translated to a treatment difference in mean change from baseline of 1.1 kg (p=0.0141). However, it was noted that the mean baseline weight for lina+pio patients was lower than that of pbo+pio patients both at baseline (pbo+pio 82.7 kg; lina+pio 78.4 kg) and at the end of the study (pbo+pio 84.0 kg; lina+pio 80.8 kg). *Biomarkers* Reductions in the homeostasis model assessment of insulin resistance (HOMA-IR) were observed for both treatment groups with respect to baseline, in line with known effect of pioglitazone to decrease insulin resistance. Still, a further decrease in insulin resistance in the lina+pio group was shown by the treatment difference of −0.32 (p=0.1623) compared with pbo+pio. Moreover, the increase from baseline to week 24 for the disposition index was significantly greater for lina+pio than for pbo+pio, with a difference in the adjusted mean change from baseline of 2.69; p=0.0101.
Safety results:	All 389 treated subjects who had received at least one dose of trial medication (treated set) were included in the analysis of safety. *Exposure* The mean exposure to study medication was 157.6 days (SD 38.8) in the pbo+pio group and 164.0 days (SD 28.5) in the lina+pio group. The median exposure for both treatment groups was 169 days. The vast majority of the patients (87.7% in the pbo+pio group and 94.2% in the lina+pio group) were exposed to study medication for >20 to 26 weeks. The duration of exposure to linagliptin was 116.3 patient years.

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Adverse events

The proportion of patients that had at least 1 AE during the trial was similar in both treatment groups, with 69 patients (53.1%) in the pbo+pio group and 136 patients (52.5%) in the lina+pio group. Most of the AEs were of mild or moderate intensity.

The system organ class (SOC) with the highest frequency of reported AEs was 'infections and infestations', with 32 patients (24.6%) in the pbo+pio group and 54 patients (20.8%) in the lina+pio group. Overall, the most frequently reported AE at the preferred term level was nasopharyngitis (8.5% pbo+pio; 9.3% lina+pio).

Adverse events in the SOC 'cardiac disorders' were reported for 3 patients (1.2%) in the lina+pio group (acute coronary syndrome, atrial fibrillation, and coronary artery disease) and in none in the pbo+pio group. AEs in the SOC 'skin and subcutaneous tissue disorders' were reported for 2 patients (1.5%) in the pbo+pio group (erythema and intertrigo) and 7 patients (2.7%) in the lina+pio group (contact dermatitis, eczema, lichen planus, photosensitivity reaction, rash, and seborrheic dermatitis). In the SOC 'vascular disorders' there were AEs reported for 3 patients (2.3%) in the pbo+pio group (hypertension) and 9 patients (3.5%) in the lina+pio group (hypertension, hypertensive crisis, hypotension, and varicose vein). 'Renal and urinary disorders' were reported for 1 patient (0.8%) in the pbo+pio group (nephropathy) and 2 patients (0.8%) in the lina+pio group (nephrolithiasis and polyuria).

Regarding AEs considered by the investigator to be related to study medication, those most frequently reported were within the SOC 'metabolism and nutrition disorders', with 2 patients (1.5%) in the pbo+pio group and 5 patients (1.9%) in the lina+pio group. At the preferred term level, the most frequently reported drug-related AE was weight increase in 1 patient (0.8) in the pbo+pio and 6 patients (2.3%) in the lina+pio group.

Adverse events leading to treatment discontinuation were reported for 5 patients (3.8%) in the pbo+pio group and 4 patients (1.5%) in the lina+pio group, 11 out of the 13 reported AEs were considered to be drug-related by the investigator.

Hypoglycaemic events were reported for 3 patients (1.2%) in the lina+pio group, versus none in the pbo+pio group. All events were symptomatic, of mild

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intensity, and were not considered to be related to the use of rescue medication. The 3 patients were aged 60 years or older.

Two events adjudicated by an independent Clinical Event Committee (CEC) were confirmed as stable angina and non-ST segment elevation myocardial infarction (NSTEMI), respectively. Both patients were in the lina+pio group.

There were no deaths in this trial. Serious adverse events (SAEs) were reported for 3 patients (2.3%) in the pbo+pio group and 8 patients (3.1%) in the lina+pio group. In the lina+pio group, SAEs were: acute coronary syndrome (CEC-confirmed NSTEMI), colonic polyp, cholelithiasis, removal of meniscus, carotid artery stenosis, varicose vein, vomiting, upper abdominal pain, and hypoesthesia. Hypoesthesia (described as an undesirable effect of pioglitazone) was the only SAE considered to be related to the study drug by the investigator. All of the SAEs required hospitalisation, and all patients recovered by the end of the trial.

During the placebo run-in period, one patient experienced an SAE which was diagnosed as pancreatic carcinoma. The SAE was considered immediately life-threatening and resulted in removal of the patient from the trial, the SAE was not considered to be related to study medication. The patient had been receiving placebo at the time of onset of the AE.

In the assessment of significant AEs based on Standard MedDRA (medical drug dictionary for drug regulatory affairs) queries (SMQs) to evaluate hypersensitivity reactions, liver toxicity, and acute renal failure, only one patient with erythema (pbo+pio group) fulfilled the criteria.

Laboratory parameters

Overall, the safety laboratory data revealed no trends of clinical relevance. There were few possibly clinically significant laboratory abnormalities reported. These included increased potassium concentrations in 3 patients (2.5%) in the pbo+pio group and 7 patients (2.8%) in the lina+pio group (highest value: 6.2 mmol/L). Very few patients had possibly clinically significant increases or decreases reported for enzyme concentrations, these included 1 patient (0.4%) in the lina+pio group with an AST value of 91 U/L (about 2.5 x ULN). Increased

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values of γ-glutamyl transferase above 3 x ULN were reported for 2 patients (1.7%) in the pbo+pio group and 1 patient (0.4%) in the lina+pio group (highest value 190 U/L, pbo+pio). With regard to creatine kinase values, increased concentrations (above 3 x ULN) were reported for 2 patients (1.7%) in the pbo+pio group and 4 patients (1.6%) in the lina+pio group (highest value: 1094 U/L, lina+pio). Three patients (1.2%) in the lina+pio group had possibly clinically significant increased amylase values (highest value 181 U/L).

Overall standard deviations for the amino-terminal fragment of B-type natriuretic peptide (NTproBNP) were observed to be large. The mean baseline value for NTproBNP for pbo+pio was 12.8 pg/mL (SD 37.1); mean changes from baseline ranged from 0.8 pg/dL at Visit 4 to −3.1 pg/dL at Visit 7. In the lina+pio group mean baseline value for NTproBNP was 9.9 pg/mL (SD 17.3); mean changes from baseline ranged from 1.4 pg/dL at Visit 4 to 0.3 pg/dL at Visit 7.

Mean values for total cholesterol, high-density lipoproteins, and low-density lipoproteins were within the normal reference range at baseline and end of treatment with only small mean changes from baseline in both treatment groups. Mean values for triglycerides were above the normal reference range for pbo+pio both at baseline (236 mg/dL [SD 145]) and end of treatment (219 mg/dL [SD 264]), and for lina+pio at baseline (228 mg/dL [SD 143]); mean values decreased with respect to baseline in both treatment groups (−18 mg/dL pbo+pio [SD 177]; −35 mg/dL lina+pio [SD 145]).

Possibly clinically significant increased triglyceride concentrations were reported for 12 patients (9.9%) in the pbo+pio group and 13 patients (5.1%) in the lina+pio group. Additionally, 1 patient (0.8%) in the pbo+pio group had an increased total cholesterol value considered possibly clinically significant.

Potential Hy's law cases were evaluated to assess possible liver-related adverse drug effects. No patients in the trial met Hy’s law criteria.

The vast majority of patients (95.7% in the pbo+pio group and 93.4% in the lina+pio group) remained with normal renal function (eGFR ≥ 90 mL/min) or mild renal impairment (eGFR 60 to 89 mL/min), based on MDRD (modification of diet in renal disease) and eCCr (estimated creatinine clearance rate, Cockcroft-Gault formula) staging, with only minor shifts in renal function staging throughout the trial.

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	Vital signs No relevant trends were observed over time in the mean changes from baseline for systolic and diastolic blood pressure or for pulse rate in either of the treatment groups. Systolic blood pressure mean changes from baseline ranged from −0.03 to 0.94 mmHg in the pbo+pio group and from −1.35 to 0.0 mmHg in the lina+pio group. Diastolic blood pressure mean changes from baseline ranged from −0.77 to 0.42 mmHg in the pbo+pio group and from −1.41 to −1.29 mmHg in the lina+pio group.
Conclusions:	Treatment with 5 mg linagliptin once daily for 24 weeks was superior to placebo in the reduction of HbA_{1c} levels, as initial combination with pioglitazone 30 mg in patients with type 2 diabetes mellitus and insufficient glycaemic control. Linagliptin was well-tolerated and the assessment of safety did not reveal major trends of clinical relevance. Very few cases of hypoglycaemia were reported in this trial on treatment with linagliptin.

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 HbA1c (%) mean change from baseline over time	Table 15.2.1.2.2: 1
Adjusted FPG (mg/dL) 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)	128	8.58	0.08	252	8.60	0.05					
Change from baseline at Week 6	128	-0.03	0.06	252	-0.41	0.04	-0.38	0.07	-0.52	-0.24	<.0001
Change from baseline at Week 12	128	-0.35	0.07	252	-0.85	0.05	-0.50	0.09	-0.67	-0.32	<.0001
Change from baseline at Week 18	128	-0.55	0.08	252	-1.06	0.06	-0.51	0.10	-0.70	-0.32	<.0001
Change from baseline at Week 24	128	-0.56	0.09	252	-1.06	0.06	-0.51	0.10	-0.71	-0.30	<.0001

* Model includes treatment, baseline HbA1c and previous anti-diabetic medication

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)	122	186.4	3.6	243	188.4	2.7					
Change from baseline at Week 6	122	-17.0	2.5	243	-33.3	1.9	-16.4	3.0	-22.3	-10.5	<.0001
Change from baseline at Week 12	122	-20.5	2.7	243	-33.8	2.0	-13.2	3.2	-19.5	-7.0	<.0001
Change from baseline at Week 18	122	-19.3	2.9	243	-33.2	2.1	-13.9	3.4	-20.5	-7.3	<.0001
Change from baseline at Week 24	122	-18.4	3.0	243	-32.6	2.2	-14.2	3.5	-21.1	-7.3	<.0001

* Model includes treatment, baseline HbA1c, baseline FPG and previous anti-diabetic medication