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:		**EudraCT No.:** 2009-013289-20	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 FEB 2013	**Trial No. / U No.:** 1218.61 / U13-3124-01	**Date of trial:** 03 Nov 2009 – 14 Mar 2012	**Date of revision:** Not applicable

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 with insufficient glycaemic control despite a therapy of metformin in combination with pioglitazone
Coordinating Investigator:	[redacted]
Trial sites:	Multi-center trial, refer to Appendix 16.1.4
Publication (reference):	Data from this trial have not been published
Clinical phase:	III
Objectives:	To investigate the efficacy, safety and tolerability of linagliptin (5 mg once daily) compared to placebo given for 24 weeks as add-on therapy to metformin in combination with pioglitazone in patients with type 2 diabetes mellitus with insufficient glycaemic control
Methodology:	Randomised, double-blind, parallel group trial with randomisation stratified by centre and baseline glycosylated haemoglobin A1 (HbA_{1c}) > or ≤ 8.5%.
No. of subjects:	
planned:	enrolled: 580 screened entered: 290; 193 linagliptin, 97 placebo
actual:	Linagliptin 5 mg: entered: 183; treated: 183; analysed (for primary endpoint): 179 Placebo: entered: 89; treated: 89; analysed (for primary endpoint): 89
Diagnosis and main criteria for inclusion:	Male and female patients diagnosed with type 2 diabetes mellitus with insufficient glycaemic control [HbA_{1c} ≥7.5% and ≤10.0%] despite treatment with metformin (≥1500mg/day or the maximum tolerated dose) or pioglitazone (45 mg/day or maximum clinically acceptable dose) for 12 weeks prior to trial entry. Patients ≥18 and <80 years of age with body mass index (BMI) ≤45 kg/m^2 were included in the trial.

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Test product:	Linagliptin
dose:	5 mg, once daily
mode of admin.:	Tablets per os
batch no.:	956146
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Tablets per os
batch no.:	4000015
Duration of treatment:	• 1-week screening period • 2-week placebo run-in • 24-week double-blind treatment with linagliptin 5 mg or placebo • 1-week follow-up
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint of this trial was the change from baseline in HbA_{1c} after 24 weeks of treatment. The secondary endpoints were: • occurrence of a treat to target response, i.e. an HbA_{1c} under treatment of <7.0% after 24 weeks of treatment; • occurrence of a treat to target response, i.e. an HbA_{1c} under treatment <6.5% after 24 weeks of treatment; • occurrence of a relative efficacy response, i.e. HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment; • HbA_{1c} reduction from baseline by visit over time; • change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment; • change from baseline in FPG by visit over time.
Safety:	Incidence and intensity of adverse events (AEs), primarily based on spontaneous AEs; withdrawal due to AEs; clinically relevant new or worsening findings in physical examination reported as AEs; changes from baseline in vital signs (blood pressure and pulse); clinically relevant new or worsening findings in 12-lead electrocardiogram reported as AEs; changes from baseline in clinical laboratory assessments; and hypoglycaemic events.

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Statistical methods:	Primary endpoint: Testing of superiority hypothesis versus placebo using analysis of covariance (ANCOVA) with treatment as a factor and baseline HbA_{1c} as a covariate. Secondary endpoints: ANCOVA (exploratory); logistic regression. Safety endpoints: descriptive statistics; logistic regression and Kaplan-Meier analysis for hypoglycaemic events.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	A total of 495 patients were enrolled and 280 patients were entered (randomised) into the trial. Data for one site (6 patients) was excluded from all pre-specified efficacy and safety analyses due to noncompliance. Overall, 272 randomised patients (89 placebo; 183 linagliptin) were included in the pre-specified efficacy and safety analyses. Of the 272 treated patients, 241 patients (88.6%) did not prematurely discontinue trial medication while 31 patients (11.4%) prematurely discontinued trial medication (14.6% placebo; 9.8% linagliptin) most frequently due to 'other' reasons (with the most frequent reason being the discontinuation of the trial in France due to removal of pioglitazone from the market). The primary endpoint in this trial was the change from baseline in HbA_{1c} after 24 weeks of treatment. There were 89 patients in the placebo group and 179 patients in the linagliptin group with baseline and on-treatment results for HbA_{1c} included in the primary analysis. After 24 weeks of treatment, the adjusted mean change from baseline in HbA_{1c} was -0.27% for the placebo group and -0.84% for the linagliptin group. The difference between the treatment groups in adjusted mean change in HbA_{1c} from baseline at Week 24 was -0.57% (95% CI: -0.83, -0.31; $p<0.0001$), demonstrating superiority of linagliptin over placebo in reduction of HbA_{1c} after 24 weeks of treatment. The adjusted mean difference between linagliptin and placebo for the change in FPG from baseline at Week 24 was −10.4 mg/dL (p=0.0280). Concerning the treat-to-target efficacy response, among patients with baseline $HbA_{1c} \geq 7.0\%$, 13.8% of the patients in the placebo group and 32.4% of the patients in the linagliptin group achieved $HbA_{1c} < 7.0\%$ after 24 weeks of treatment. The odds of achieving HbA_{1c} levels <7.0% for patients with baseline $HbA_{1c} \geq 7.0\%$ were almost 3 times higher with linagliptin treatment than with

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Efficacy / clinical pharmacology results (continued):	placebo treatment (odds ratio: 2.939, p=0.0033). Among patients with baseline HbA_{1c} ≥6.5%, 5.6% of the patients in the placebo group and 19.1% of the patients in the linagliptin group achieved HbA_{1c} <6.5% at Week 24. The odds of achieving HbA_{1c} levels <6.5% in patients with baseline HbA_{1c} ≥6.5% was almost 4 times greater with linagliptin treatment (odds ratio: 3.902, p=0.0074). Overall, a higher frequency of patients in the linagliptin group had an HbA_{1c} reduction of at least 0.5%. At Week 24, the odds to achieve an HbA_{1c} reduction of at least 0.5% were 2 times greater for patients treated with linagliptin compared to treatment with placebo (odds ratio = 2.059, p = 0.0071).
Safety results:	There were 7 serious AEs (SAEs), including one SAE in the placebo group that was fatal, reported as single SAEs (3.4% placebo; 2.2% linagliptin) without any trends noted. The fatality in the placebo group was confirmed by the Clinical Event Committee (CEC), the only adjudicated event, as a cardiovascular death and myocardial infarction. There were no hepatic, pancreatitis, renal, or cutaneous skin lesion AEs of Special Interest that occurred during the treatment period. One hypersensitivity reaction AE of Special Interest (pruritis, 0.5%) occurred in the linagliptin group. Other significant AEs [according to International Conference on Harmonisation (ICH) E3 guideline] were not clinically meaningful (0% placebo; 2.2% linagliptin). Overall, 48.3% of patients in the placebo group and 62.3% of patients in the linagliptin group experienced AEs. Although the incidence of AEs was higher in the linagliptin group, the higher incidence of any AEs was not due to any discernible patterns of AEs, but rather due to a wide range of AEs. The majority of the AEs were mild or moderate; 2.2% or less of patients (1.1% placebo; 2.2% linagliptin) experienced severe AEs. The proportion of patients experiencing hypoglycaemic events (5.6% placebo; 5.5% linagliptin) was comparable. No patients had severe episodes of hypoglycaemic events requiring assistance. The number of related AEs, as assessed by the investigator, occurred in 13.5% of the patients for the placebo group and in 11.5% of the patients for the linagliptin group. There were very few patients who experienced AEs that led to premature discontinuation (2.2% placebo; 2.7% linagliptin). There were no clinically meaningful differences between the treatment groups for these categories of AEs.

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Conclusions:	Linagliptin as add-on therapy to metformin and pioglitazone produced significant and clinically meaningful improvements in glycemic control, including a statistically significant reduction in the change from baseline in HbA1c (HbA1c after 24 weeks of treatment) compared to placebo. Linagliptin demonstrated a favorable safety profile, including no increased risk for hypoglycemia and no meaningful change in body weight. Linagliptin was well tolerated and no safety concerns developed.

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 secondary 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} (%) over time	Table 15.2.1.2.2: 1
FPG (mg/dL) over time	Table 15.2.2.1: 6
Logistic regression of HbA_{1c} lowering by ≥0.5% at week 24	Table 15.2.2.4: 1
Patients with HbA_{1c} lowering by ≥0.5% at week 24	Table 15.2.2.4: 2

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)	89	8.47	0.08	179	8.39	0.06					
Change from baseline at Week 6	89	-0.19	0.11	179	-0.60	0.09	-0.41	0.10	-0.61	-0.21	<.0001
Change from baseline at Week 12	89	-0.28	0.12	179	-0.82	0.10	-0.54	0.13	-0.79	-0.28	<.0001
Change from baseline at Week 18	89	-0.37	0.12	179	-0.91	0.10	-0.54	0.13	-0.80	-0.29	<.0001
Change from baseline at Week 24	89	-0.27	0.13	179	-0.84	0.11	-0.57	0.13	-0.83	-0.31	<.0001

* Model includes treatment,baseline HbA1c and random centre

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)	86	151.3	4.9	175	148.9	3.5					
Change from baseline at Week 6	86	12.4	5.4	175	-3.3	4.6	-15.7	4.5	-24.5	-6.8	0.0006
Change from baseline at Week 12	86	3.8	4.6	175	-7.1	3.6	-10.9	4.7	-20.2	-1.7	0.0210
Change from baseline at Week 18	86	-2.4	4.1	175	-8.6	2.8	-6.2	5.0	-16.0	3.6	0.2137
Change from baseline at Week 24	86	0.1	3.8	175	-10.3	2.7	-10.4	4.7	-19.6	-1.1	0.0280

* Model includes treatment, baseline HbA1c, baseline FPG and centre as random

Table 15.2.2.4: 1 Logistic regression of HbA1c lowering by 0.5% at week 24 - FAS (NCF)

Factor	Odds ratio	95% CI LL	95% CI UL	Wald Chi-Sq	df	p-value
Treatment Group						
Linagliptin : Placebo	2.059	1.216	3.485	7.235	1	0.0071
Baseline HbA1c						
Odds ratio per 1% increase	1.454	1.059	1.997	5.366	1	0.0205

Table 15.2.2.4: 2 Number of patients with HbA1c lowering by 0.5% at week 24 - FAS (NCF)

	Placebo (N=89)				Linagliptin (N=179)			
	Hba1C Reduction >=0.5%				Hba1C Reduction >=0.5%			
	No	Yes	Missing	Total	No	Yes	Missing	Total
Baseline HbA1C (categorical) [N (%)]								
N	45 (50.6)	44 (49.4)	0 (0.0)	89 (100.0)	61 (34.1)	117 (65.4)	1 (0.6)	179 (100.0)
<7.0%	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	3 (100.0)	0 (0.0)	0 (0.0)	3 (100.0)
7.0% to <8.0%	14 (60.9)	9 (39.1)	0 (0.0)	23 (100.0)	21 (36.8)	36 (63.2)	0 (0.0)	57 (100.0)
8.0% to <9.0%	20 (48.8)	21 (51.2)	0 (0.0)	41 (100.0)	22 (29.7)	52 (70.3)	0 (0.0)	74 (100.0)
>=9.0%	9 (39.1)	14 (60.9)	0 (0.0)	23 (100.0)	15 (33.3)	29 (64.4)	1 (2.2)	45 (100.0)