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.:** 2009-013549-27	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 MAR 2011	**Trial No. / U No.:** 1218.62 / U11-3093-01	**Date of trial:** 12 NOV 2009 – 28 SEP 2010	**Date of revision:** Not applicable

Title of trial:	A randomised, double-blind, placebo-controlled, 3 parallel group efficacy and safety study of linagliptin 2.5 mg twice daily versus 5 mg once daily over 12 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes mellitus and insufficient glycaemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, cf. Appendix 16.1.4.
Publication (reference):	Data of this study have not been published.
Clinical phase:	IIb
Objectives:	To investigate the influence of different dosage regimens (twice daily versus once daily versus placebo) on the efficacy and safety of linagliptin administered orally as add-on therapy to metformin.
Methodology:	Randomised, double-blind, placebo-controlled, parallel group comparison.
No. of subjects:	
planned: 451	Enrolled: 771
	Randomised: 491
actual: 491	Linagliptin 2.5 mg bid: entered: 223 treated: 223 analysed (full analysis set): 214 Linagliptin 5 mg qd: entered: 224 treated: 224 analysed (full analysis set): 221
	Placebo: entered: 44 treated: 44 analysed (full analysis set): 43
Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus insufficiently controlled (HbA_{1c} ≥7.0-≤10.0% at Visit 2) on metformin (at least 1500 mg/day, bid or maximum tolerated dose if lower than this), age ≥18 and ≤80 years, BMI range: ≤45 kg/m^2
Test product:	Linagliptin tablet
dose:	2.5 mg bid

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mode of admin.:	p.o.
batch no.:	B081004241
Reference therapy:	Linagliptin tablet
dose:	5 mg
mode of admin.:	p.o.
batch no.:	956146
Reference therapy:	Placebo tablet
dose:	NA
mode of admin.:	p.o.
batch no.:	B091001080 (lina 2.5 placebo) 4000015 (lina 5 placebo)
Duration of treatment:	Double-blind treatment with linagliptin 2.5 mg bid, or 5 mg qd, or placebo for 12 weeks, followed by 1 week follow-up after study drug termination. Metformin was administered as background therapy in an unchanged total daily dosage throughout the trial (including wash-out, placebo run-in, 12-week randomised treatment, and follow-up phases).
Criteria for evaluation:	
Efficacy / clinical pharmacology:	• HbA_{1c} change from baseline after 12 weeks of treatment • Occurrence of relative efficacy response (HbA_{1c} lowering by at least 0.5% after 12 weeks of treatment) • The occurrence of a treat to target efficacy response (HbA_{1c} <7.0%) after 12 weeks of treatment • The occurrence of a treat to target efficacy response (HbA_{1c} <6.5%) after 12 weeks of treatment • Change from baseline in HbA_{1c} by visit over time • Change from baseline in FPG after 12 weeks of treatment • Change from baseline in FPG by visit over time • Use of rescue therapy.

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Safety:	• Frequency of adverse events and hypoglycaemic events • Changes in vital signs and body weight • Change from baseline in clinical laboratory values
Statistical methods:	For the primary analysis of HbA_{1c} change from baseline after 12 weeks, an analysis of covariance (with factors for treatment, number of prior antidiabetics and baseline HbA_{1c} as a linear covariate) was used to test the following comparisons in the order shown (to maintain the overall false positive rate at 0.05): • Superiority of linagliptin 2.5 mg bid. vs. placebo. If shown, then: • Non-inferiority of linagliptin 2.5 mg bid. treatment versus reference therapy with linagliptin 5 mg qd using a pre-specified non-inferiority margin of 0.35%. If shown, then: • Superiority of linagliptin 5 mg qd vs. placebo Sensitivity analyses were performed to investigate the impact of missing data, the use of rescue medication, and the presence of important protocol violations on the primary analysis. Fasting plasma glucose change from baseline after 12 weeks was analysed similarly to HbA_{1c} with FPG at baseline as an additional linear covariate. Descriptive statistics were presented for other secondary endpoints and safety parameters.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	A total of 771 patients were enroled by 81 centres in Asia, Europe, and North America. Of the enrolled patients, 491 patients were randomised in a 1:5:5 ratio to receive treatment with either placebo (44 patients), linaglipin 2.5 mg bid (223 patients) or linaglipin 5 qd (224 patients). Of the 491 patients treated with randomised study medication, 464 patients (94.5%) completed the planned 12-week treatment period and 27 patients (5.5%) prematurely discontinued the trial medication. Overall, the demographic profile was balanced between the treatment groups. More than half of the population was male (total 57.0%). Nearly two thirds of the population was White (total 65.4%) and about one third was Asian (total

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33.8%).

The mean age was 58.6 years (total) with the largest proportion of patients being 65 years of age or younger (total 69.5%). All three treatment groups had comparable distribution of patients across age groups. In total, the mean weight was 81.0 kg and the mean BMI was 29.6 kg/m^2. Almost three-quarters of the patients were pre-treated with metformin monotherapy (71.3% total), with comparable percentages seen across treatment groups. A total of 28.7% of patients were pre-treated with combination therapy (metformin and 1 'other' OAD) prior to study entry and underwent a washout period for the 'other' OAD; sulphonylurea (23.8% total) was the most commonly prescribed previous OAD in addition to metformin.

The baseline mean HbA_{1c} percent values were comparable between the treatment groups and the overall mean HbA_{1c} was 7.97%.

Primary endpoint

Superiority of both linagliptin treatment groups (lina 2.5 bid and lina 5 qd) over placebo in HbA_{1c} reduction from baseline at 12 weeks was shown, as well as lina 2.5 bid being non-inferior to lina 5 qd according to the pre-specified criterion in the protocol. The primary analysis used FAS (LOCF) consisting of 478 patients (placebo: 43 patients; lina 2.5 bid: 214 patients; lina 5 qd: 221 patients).

The adjusted mean treatment difference in HbA_{1c} from baseline to Week 12 with lina 2.5 bid compared to placebo was -0.74% (95% CI -0.97, -0.52), indicating superiority of lina 2.5 bid over placebo ($p<0.0001$) in the reduction of HbA_{1c}.

The adjusted mean treatment difference in HbA_{1c} from baseline to Week 12 with lina 2.5 bid compared to lina 5 qd was 0.06% (95% CI -0.07, 0.19), indicating non-inferiority of lina 2.5 bid as compared to lina 5 qd in the reduction of HbA_{1c} according to the pre-specified protocol definition.

The upper bound of the 95% CI for the difference between lina 2.5 bid and lina 5 qd was 0.19, which is small enough that non-inferiority would also have been concluded using a stricter non-inferiority definition than the 0.35 margin pre-specified in the protocol. The adjusted mean treatment difference in HbA_{1c} from baseline to Week 12 with lina 5 qd compared to placebo was -0.80% (95% CI -1.02, -0.58), indicating superiority of lina 5 qd over placebo

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($p<0.0001$) in the reduction of HbA_{1c}. A conservative within-study estimate for the proportion of the lina 5 qd effect preserved by lina 2.5 bid would be 67%; calculated as follows: (0.58 - 0.19)/0.58 = 67%.

Sensitivity analyses using the PPS (LOCF), PPS-completers (OC), FAS-completers (OC), and FAS using values obtained after administration of rescue medication all gave results which were consistent with those from the primary analysis.

Secondary endpoints

The analyses performed to assess how many patients reached target HbA_{1c} levels of <7.0% or <6.5% after 12 weeks of treatment (i.e., had absolute efficacy response) and how many patients had a ≥0.5% reduction after 12 weeks of treatment (i.e. had relative efficacy response) were all in favour of lina 2.5 bid and lina 5 qd compared with placebo. For patients with a baseline HbA_{1c} ≥7.0%, patients on treatment with lina 2.5 bid and lina 5 qd were more likely than those on treatment with placebo to achieve an HbA_{1c} value below 7.0% after 12 weeks (10.0% placebo; 34.0% lina 2.5 bid; 33.0% lina 5 qd). For patients with baseline HbA1c ≥6.5%, the likelihood of achieving an HbA_{1c} reduction to <6.5% at 12 weeks was higher in the linagliptin groups than in the placebo group (0.0% placebo; 12.7% lina 2.5 bid; 11.8% lina 5 qd). Likewise, patients treated with lina 2.5 bid and lina 5 qd were more likely to achieve a HbA_{1c} reduction from baseline of ≥0.5% at 12 weeks than patients in the placebo group (16.3% placebo, 55.1% lina 2.5 bid, 59.7% lina 5 qd).

The adjusted mean change from baseline in reduction of HbA_{1c} over time demonstrated a greater reduction in HbA_{1c} at each time point in the linagliptin treatment groups as compared to placebo.

Lina 2.5 bid and lina 5 qd were superior over placebo in FPG reduction from baseline, with a treatment difference compared to placebo in the adjusted mean change from baseline at 12 weeks for lina 2.5 bid of -13.7 mg/dL (95% CI: -22.7, -4.7; p=0.0029) and -17.8 mg/dL (95% CI: -26.7, -8.8; p=0.0001) for lina 5 qd. The adjusted mean change from baseline in FPG over time demonstrated a greater reduction in FPG at each time point in the linagliptin treatment groups as compared to placebo.

Patients on treatment with lina 2.5 bid and lina 5 qd were less likely to require the use of rescue therapy than patients on treatment with placebo (7.0% placebo,

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	3.7% lina 2.5 bid and 1.8% lina 5 qd), although the proportion of patients who used rescue medication in all groups was small .
Safety results:	All 491 treated patients who took at least one dose of study medication during the randomised treatment period (treated set) were included in the analysis of safety. **Exposure** The median exposure was 85 days in all three treatment groups. The total exposure was 10.1 patient years in the placebo group, 50.0 years in the lina 2.5 bid group and 51.6 years in the lina 5 qd group. **Adverse events** Overall, the percentages of patients reported with AEs were as follows: 38.6% of patients in the placebo group, 43.0% in the lina 2.5 bid group and 34.8% in the lina 5 qd group. The majority of the AEs were of mild or moderate intensity. Patients with AEs were most frequently reported in the SOCs gastrointestinal disorders (ranging from 4.9% to 9.4%), infections and infestations (ranging from 11.4% to 14.3%), and musculoskeletal and connective tissue disorders (ranging from 7.6% to 11.4%). Further AEs which are of interest in the development of antidiabetic drugs or are seen in connection with DPP-4 inhibitors occurred with a frequency of less than 2% on PT level in the SOCs cardiac disorders (with single patient events noted), renal and urinary disorders, and skin and subcutaneous tissue disorders. There was no case of pancreatitis reported in any of the treatment groups. In the placebo group, 2 patients (4.5%) were reported with drug-related AEs (as assessed by the investigator), in the lina 2.5 bid group 19 patients (8.5%), and in the lina 5 qd group 3 patients (1.3%). Drug-related AEs occurring with a frequency of at least 2% on SOC level, were in the SOCs gastrointestinal disorders (gastritis and nausea being the most frequently reported PT) and metabolism and nutrition disorders (hypoglycaemia being the most frequently reported PT). No patients in the placebo group reported an AE that led to discontinuation. In the lina 2.5 bid group 8 patients (3.6%) were reported with 15 AEs leading to discontinuation and in the lina 5 qd group, 3 patients (1.3%) were reported with AEs leading to discontinuation; 6 of the 18 events were assessed as not related to

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the study medication. In addition, AEs leading to discontinuation were checked manually for any changes in vital signs (bradycardia, tachycardia, hypertension, and hypotension). No such events were reported in any of the treatment groups.

Investigator-defined hypoglycaemic events were reported by 1 patient (2.3%) in the placebo group, 7 patients (3.1%) in the lina 2.5 bid group, and 2 patients (0.9%) in the lina 5 qd group. No patient required assistance and only 1 received rescue medication at the time of the event.

CEC-confirmed events were reported for 1 patient in the lina 2.5 bid group (unstable angina) and 1 patient in the lina 5 qd group (ST elevation MI [STEMI]).

There were no fatal events during this study. Overall, the number of patients with SAEs was low: 0 patients (0.0%) in the placebo group, 9 patients (4.0%) in the lina 2.5 bid group, and 5 patients (2.2%) in the lina 5 qd group. All SAEs except one were considered as not being drug-related; one patient in the lina 5 qd group was reported with an acute myocardial infarction which was assessed as drug-related by the investigator. Eight of the nine patients with an SAE in the lina 2.5 bid group recovered; one patient did not recover from left fibula fracture. In the lina 5 qd group, all patients recovered from the reported SAEs.

One patient (0.4%) in the lina 5 qd group experienced an exacerbation of asthma that was determined to be a pre-defined hypersensitivity reaction. Cardiac and cerebrovascular events were reported by 0 patients (0.0%) in the placebo group, 1 patient (0.4%) in the lina 2.5 bid group, and 3 patients (1.3%) in the lina 5 qd group. In the lina 2.5 bid group, the cardiac and cerebrovascular event was angina pectoris. In the lina 5 qd group, 1 patient reported acute myocardial infarction, 1 (different) patient reported myocardial infarction and 1 patient reported myocardial ischaemia. Only 2 events were confirmed by adjudication (unstable angina pectoris and acute myocardial infarction). Hepatic events were reported for 0 patients (0.0%) in the placebo group, 2 patients (0.9%) in the lina 2.5 bid group, and 2 patients (0.9%) in the lina 5 qd group. In the lina 2.5 bid group, the hepatic events were ALT increased and transaminases increased. In the lina 5 qd group, the reported AEs were ALT increased and increased AST. No severe cutaneous adverse reactions were reported in this study and no renal AEs were noted during the treatment phase of the study.

'Other significant' AEs (based upon ICH E3) were reported by 0 patients (0.0%)

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	in the placebo group, 6 patients (2.7%) in the lina 2.5 bid group, and 2 patients (0.9%) in the lina 5 qd group. All events led to treatment discontinuation. **Laboratory parameters** Few patients were reported with PCSAs and none were considered as an AE or determined to be clinically meaningful. There were no patients fulfilling the criteria of Hy's law in this study and no notable differences between treatments were observed for changes in renal function. **Vital signs** Overall, no clinically significant differences between the treatment groups were observed in blood pressure and pulse rate from baseline to end of treatment. The majority of patients had inconspicuous values at the end of treatment and only a small proportion of patients shifted from inconspicuous to conspicuous values at end of treatment (≤2.7% for SBP, ≤0.4% for DBP in all treatment groups), with no relevant differences between treatments (only 2 patients had abnormal pulse rates).
Conclusions:	Treatment with linagliptin 2.5 mg bid and linagliptin 5 mg qd was superior to placebo in the reduction of HbA_{1c} and the reduction of fasting plasma glucose levels from baseline to 12 weeks, as add-on therapy to metformin bid in patients with type 2 diabetes mellitus and insufficient glycaemic control (on metformin monotherapy alone or previously treated with metformin in combination with another anti-diabetic therapy). In addition, linagliptin 2.5 mg bid met the pre-specified criterion on non-inferiority in comparison to linagliptin 5 mg qd in the reduction of HbA_{1c} from baseline to 12 weeks, and preserved at least 67% of the lina 5 qd effect estimated in this study. The assessment of safety did not reveal any major trends of clinical relevance and few cases of hypoglycaemia were reported in this trial in all treatment groups.

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: 3
FPG (mg/dL) change from baseline over time	Table 15.2.2.1: 4

Table 15.2.1.2.2: 3 Adjusted means for HbA1c (%) change from baseline over time from mixed model repeated measurements analysis - FAS

	Placebo	Lina 2.5 bid	Lina 5 qd
Baseline			
Unadjusted mean (SE)	7.92 (0.11)	7.96 (0.05)	7.98 (0.05)
Week 6			
Adjusted mean (SE)	0.32 (0.08)	-0.34 (0.04)	-0.34 (0.04)
Difference: Linagliptin - Placebo			
Adjusted mean (SE)		-0.66 (0.09)	-0.66 (0.09)
95% CI		(-0.83,-0.48)	(-0.84,-0.49)
p-value		<.0001	<.0001
Difference: Lina 2.5 - Lina 5			
Adjusted mean (SE)		0.00 (0.05)	
95% CI		(-0.10, 0.10)	
Week 12			
Adjusted mean (SE)	0.27 (0.11)	-0.51 (0.05)	-0.55 (0.05)
Difference: Linagliptin - Placebo			
Adjusted mean (SE)		-0.77 (0.12)	-0.82 (0.12)
95% CI		(-1.00,-0.54)	(-1.05,-0.59)
p-value		<.0001	<.0001
Difference: Lina 2.5 - Lina 5			
Adjusted mean (SE)		0.05 (0.07)	
95% CI		(-0.08, 0.18)	

Mixed model includes treatment, continuous baseline HbA1c, number of prior OADs in addition to background metformin, week repeated within patient, week by treatment interaction.

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

	Placebo	Lina 2.5 bid	Lina 5 qd
Baseline			
Unadjusted mean (SE)	166.2 (6.3)	164.1 (2.9)	165.8 (2.4)
Week 6			
Adjusted mean (SE)	-1.2 (4.1)	-17.8 (1.9)	-20.1 (1.8)
Difference: Linagliptin - Placebo			
Adjusted mean (SE)		-16.6 (4.4)	-18.9 (4.4)
95% CI		(-25.3, -7.8)	(-27.6,-10.2)
p-value		0.0002	<.0001
Difference: Lina 2.5 - Lina 5			
Adjusted mean (SE)		2.3 (2.5)	
95% CI		(-2.6, 7.3)	
Week 12			
Adjusted mean (SE)	-8.7 (5.0)	-18.7 (2.3)	-23.9 (2.2)
Difference: Linagliptin - Placebo			
Adjusted mean (SE)		-10.0 (5.4)	-15.3 (5.4)
95% CI		(-20.6, 0.6)	(-25.8, -4.7)
p-value		0.0653	0.0047
Difference: Lina 2.5 - Lina 5			
Adjusted mean (SE)		5.3 (3.0)	
95% CI		(-0.7, 11.3)	

Mixed model includes treatment, continuous baseline HbA1c, continuous baseline fasting plasma glucose, number of prior OADs in addition to background metformin, week repeated within patient, week by treatment interaction.