Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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 metformin therapy
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial: 82 centres in 10 countries (Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden and USA)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this study was to investigate efficacy and safety of linagliptin 5 mg versus placebo administered for 24 weeks as add-on therapy to metformin in patients with type 2 diabetes mellitus with insufficient glycaemic control.
Methodology:	Randomised, placebo-controlled, double-blind, parallel-group comparison of 2 groups over 24 weeks. Before randomisation, patients pre-treated with one additional oral antidiabetic agent (apart from metformin) 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 additional oral antidiabetic agent performed only a 2-week placebo run-in period.
No. of subjects:	
planned:	Entered: 600
actual:	Enrolled: 1268
	Linagliptin 5 mg Entered: 524 treated: 523 analysed (for primary endpoint): 513
	Placebo Entered: 177 treated: 177 analysed (for primary endpoint): 175

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Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus and insufficient glycaemic control despite therapy with ≥1500 mg/day (or maximum tolerated dose) metformin (patients undergoing washout of previous antidiabetic medication: 6.5%≤ glycosylated haemoglobin [HbA_{1c}] ≤9.0%; patients not undergoing washout of previous antidiabetic medication: 7.0%≤ HbA_{1c} ≤10.0%); age ≥18 and ≤80 years; BMI ≤40 kg/m^2
Test product:	Linagliptin
dose:	5 mg once daily
mode of admin.:	Tablet, oral
batch no.:	B071001951, B071003944
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Tablet, oral
batch no.:	B071002355 (575992), B071003943
Duration of treatment:	Six-week washout period including placebo run-in during the last 2 weeks (patients pre-treated with 1 additional oral antidiabetic agent apart from metformin) or 2-week placebo run-in (patients not previously treated with an additional oral antidiabetic agent other than metformin); 24-week treatment period; 1-week follow-up period. Background medication (metformin) was taken during the entire trial duration (including the washout 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%), and a meal tolerance test (MTT): 2-hour post-prandial glucose (2hPPG) change from baseline after 24 weeks of treatment.

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Safety:	Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory parameters, home blood glucose monitoring
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: ANCOVA for all secondary endpoints except for use of rescue medication (logistic regression and Kaplan Meier). Mainly descriptive statistics were used. Applied inferential statistical approaches were used in an explorative, descriptive manner.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

In this study, 1268 patients were enrolled in 82 centres in Asia, Europe, North America and South America. A total of 701 patients were randomised in a 1:3 ratio to receive either placebo (177 patients) or linagliptin 5 mg (524 patients) in addition to ongoing background metformin therapy. About 45% 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 700 patients (177 patients placebo; 523 patients linagliptin) were treated with randomised study medication. Of those, 53 patients (7.6%) prematurely discontinued trial medication (7.9% placebo; 7.5% linagliptin). The most frequent reason for discontinuation was refusal to continue receiving study medication (2.3% placebo; 2.5% linagliptin).

The demographic baseline characteristics of the treated patients were comparable between the treatment groups. Although there were slightly more males (54.1%) in the trial, the male-female ratio in the patient population was consistent across the treatment groups. The majority of patients were either white (76.1%) or Asian (20.9%). In both treatment groups, around 20% of the patients were of Hispanic/Latino origin. The mean age was 56.5 years. The majority of patients were under 65 years of age (76.8% in the placebo and 78.4% in the linagliptin treatment group). Mean baseline body mass index was comparable between treatment groups (30.1 kg/m^2 placebo; 29.9 kg/m^2 linagliptin). At baseline, 59.1% of patients had a normal renal function (eGFR $\geq$ 90 mL/min), 34.0% had mild renal impairment (eGFR 60 to 89 mL/min), while 3.3% had moderate renal impairment (eGFR 30 to 59 mL/min).

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Baseline mean HbA_{1c} was comparable between both treatment groups (8.0% [SD 0.88] placebo; 8.1% [SD 0.86] linagliptin). Likewise, baseline mean FPG was also comparable between the treatment groups (166.4 mg/dL [SD 41.9] placebo; 169.6 mg/dL [43.5] linagliptin). The proportions of patients in each of the prior oral antidiabetic drug (OAD) groups were similar across the treatment groups, with an overall 68.6% of the patients having received 1 prior OAD (metformin), and 31.4% having received more than 1 prior OAD, in which case the most frequently (26.9%) used combination was a sulfonylurea in addition to metformin.

The efficacy endpoint analyses were performed on the full analysis set (FAS) of patients which comprised all patients who had a baseline and at least one on-treatment HbA_{1c} measurement available (n=688). The last observation carried forward (LOCF) approach was applied (placebo: 175 patients; linagliptin 513 patients) to impute missing data.

Primary endpoint

Superiority of linagliptin over placebo was demonstrated for the primary endpoint by a treatment difference in HbA_{1c} mean change from baseline of −0.64% (SE: 0.07; 95% CI: −0.78, −0.50; $p<0.0001$) after 24 weeks of treatment. The adjusted change from baseline in the linagliptin group was −0.49% (SE 0.04) compared with 0.15% (SE 0.06) in the placebo group.

Sensitivity analyses confirmed the superiority of linagliptin shown in the primary efficacy analysis. One of these sensitivity analyses, a mixed model for repeated measurement analysis performed on the FAS applying an observed cases approach (without imputation of missing data) showed a significant ($p <0.0001$) difference between both treatments in the adjusted mean HbA_{1c} change from baseline over the entire treatment duration. This difference increased over time from 6 weeks (−0.44%) to 18 weeks (−0.69%) and remained unchanged up to the end of treatment at 24 weeks (−0.67%). A significant difference in favour of linagliptin was observed in the adjusted mean HbA_{1c} change from baseline of −0.65% ($p<0.0001$) at 24 weeks in patients receiving a total daily dose of metformin of 1500 mg or above.

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Secondary endpoints

Linagliptin was superior to placebo in FPG reduction from baseline. The adjusted mean change from baseline was 10.5mg/dL (SE 2.8) for placebo and −10.7 (SE 1.7) for linagliptin. The difference in the adjusted mean change from baseline at 24 weeks was −21.1 mg/dL (SE: 3.1; 95% CI: −27.3, −15.0; p<0.0001). Sensitivity analyses confirmed this result.

In the assessment of the absolute efficacy response (patients reaching target HbA_{1c} levels of <7.0% or <6.5% after 24 weeks of treatment), and in the assessment of relative efficacy response (patients with ≥ 0.5% HbA_{1c} reduction) after 24 weeks of treatment, linagliptin was also shown to be superior to placebo. For patients with a baseline HbA_{1c} greater or equal to 7.0%, those in the linagliptin group were more likely than patients in the placebo group to achieve an HbA_{1c} below 7.0% after 24 weeks (9.2% placebo versus 26.2% linagliptin; odds ratio 4.395, p <0.0001). For patients with baseline HbA_{1c} greater or equal to 6.5% the likelihood of achieving an HbA_{1c} below 6.5% at 24 weeks was higher in the linagliptin group than in the placebo group (2.3% placebo versus 10.4% linagliptin; odds ratio 5.456, p=0.0016). Patients in the linagliptin group were more likely than patients in the placebo group to have HbA_{1c} values reduced by at least 0.5% at 24 weeks (21.7% placebo versus 49.7% linagliptin; odds ratio 3.754, p <0.0001).

The change in post-prandial glucose after 2h was analysed in the MTT set (patients with adequate MTT results available at the beginning and end of the randomised treatment period). The adjusted means for the change of baseline in 2hPPG was18.3 mg/dL (SE 12.9) for placebo and −48.9 mg/dL (SE 7.4) for linagliptin. The resulting difference in the adjusted mean change from baseline in 2hPPG [mg/dL] at week 24 between the 2 treatment groups was −67.13 mg/dL (SE 3.9; p<0.0001), in favour of linagliptin. This result was consistent with the results of the primary and secondary endpoints.

Other efficacy endpoints

The patients on treatment with linagliptin were less likely to require the use of rescue therapy than patients on treatment with placebo (18.9% placebo versus 7.8% linagliptin), with an associated odds ratio of 0.276 (p=0.0001).

The change in the body weight from baseline to 24 weeks was similar between

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	the 2 treatment groups (−0.5 kg placebo; −0.4 kg linagliptin), with a difference in the adjusted mean change from baseline of 0.04 Kg (SE 0.33; p=0.9095). *Biomarkers* A significant difference (p=0.0005) in the adjusted mean change from baseline in HOMA-%B (homeostasis model assessment for insulin secretion) at 24 weeks in the log-scale was 1.26 (mU/L) / (mmol/L), based on the log-transformed data. There were no statistically significant differences between the treatment groups in the other biomarkers analysed (HOMA index for insulin resistance, and disposition index). Although not statistically significant (p=0.4053), the difference between treatments in the adjusted mean change from baseline observed for the disposition index of 4.50 (SE 5.40) suggested an improved β-cell function in favour of linagliptin. *MTT parameters* A statistically significant difference between linagliptin and placebo in the adjusted mean change from baseline in total glucose AUC was shown, with a difference of −5.35 mmol*h/L (p<0.0001) at 24 weeks. This result was consistent with the results of the primary and secondary endpoints.
Safety results:	All 700 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 mean exposure to linagliptin was 167 days. A majority of the patients, 84.2% in the placebo group and 86.4% in the linagliptin group, were exposed to study medication for >20 to 26 weeks (around the planned exposure time of 24 weeks). The duration of exposure to linagliptin was 238.6 patient years. *Adverse events* The proportions of patients with at least 1 AE reported during the randomised treatment period were similar for both treatment groups (55.4% placebo; 52.8% linagliptin). The system organ class (SOC) with the highest frequency of reported AEs was 'infections and infestations', with nearly identical proportions of patients in both

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treatment groups (38 patients [21.5%] placebo; 112 patients [21.4%] linagliptin). Overall, the most frequently reported AE at the preferred term level was hyperglycaemia (26 patients [14.7%] placebo; 27 patients [5.2%] linagliptin), followed in frequency order by nasopharyngitis (9 patients [5.1%] placebo; 27 patients [5.2%] linagliptin) and urinary tract infection (7 patients [4.0%] placebo; 16 patients [3.1%] linagliptin).

AEs classified as 'cardiac disorders', were reported for 1 patient (0.6%) in the placebo group (angina pectoris) and 12 patients (2.3%) in the linagliptin group. In the linagliptin group reported AEs were palpitations (5 patients), angina pectoris, tachycardia (2 patients), atrial fibrillation, myocardial ischaemia, ventricular extrasystoles and 1 patient with myocardial infarction and angina pectoris. AEs classified as 'skin and subcutaneous tissue disorders' were reported for 5 patients (2.8%) in the placebo group and 18 patients (3.4%) in the linagliptin group. For linagliptin AEs in this SOC were: pruritus (5 patients), hyperhidrosis (3 patients), rash (2 patients), skin ulcer, dermatitis (2 patients), acne, blister, eczema, hyperkeratosis, neurodermatitis, pruritic rash, skin exfoliation, skin fissures, skin lesion, and vitiligo. Adverse events classified as 'vascular disorders' were reported for 7 patients (4.0%) in the placebo group and 22 patients (4.2%) in the linagliptin group. In this SOC, the most frequently reported AE was hypertension, with very similar proportions in both treatment groups (6 patients [3.4%] placebo; 17 patients [3.3%] linagliptin).

Most of the AEs were of mild or moderate intensity. Adverse events of severe intensity were reported in 2 patients (1.1%) in the placebo group and 11 patients (2.1%) in the linagliptin group.

Adverse events considered to be drug-related by the investigator were reported for 19 patients (10.7%) in the placebo group, and 36 patients (6.9%) in the linagliptin group. The most frequently reported investigator-defined drug-related AE was hyperglycaemia, affecting 4 patients (2.3%) in the placebo group and 5 patients (1.0%) in the linagliptin group, followed in frequency order by hypoglycaemia (4 patients [2.3%] placebo;. 2 patients [0.4%] linagliptin).

Adverse events leading to discontinuation of trial medication were reported for 3 patients (1.7%) in the placebo group and 8 patients (1.5%) in the linagliptin group.

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Hypoglycaemic episodes were reported for 5 patients (2.8%) in the placebo group and 3 patients (0.6%) in the linagliptin group. In the linagliptin group, all 3 episodes were asymptomatic, and 2 of the events were considered to be drug-related by the investigator. In the placebo group, 4 of the 5 patients that experienced hypoglycaemia had been receiving rescue medication (sulfonylurea) at the time of onset, while all 3 patients on treatment with linagliptin experienced hypoglycaemia in the absence of rescue medication. All hypoglycaemic events were of mild intensity. During the trial, cardiac and cerebrovascular events confirmed by an independent Clinical Event Committee (CEC) for patients in the placebo group were stable angina (1 patient) and non-fatal acute ischaemic stroke (1 patient). In the linagliptin group, CEC-confirmed events were 'non-ST elevation' myocardial infarction (1 patient), stable angina (1 patient), and unstable angina (1 patient).

There were no deaths reported in this trial. Serious adverse events were reported for 4 patients (2.3%) in the placebo group and 18 patients (3.4%) in the linagliptin group. These were more frequently reported within the SOC 'renal and urinary disorders', with 4 patients (0.8%) in the linagliptin group and none in the placebo group. In the linagliptin group, reported SAEs were: blebitis, gastroenteritis, viral gastroenteritis, angina pectoris, myocardial infarction, atrial fibrillation, myocardial ischaemia, hypertension, bronchial hyperreactivity, pulmonary embolism, dyspepsia, intervertebral disc protrusion, ureteric calculus (2 patients), renal mass, nephrolithiasis (2 patients), non-cardiac chest pain, avulsion fracture, ulna fracture, and snake bite. The myocardial ischaemia was considered as potentially life threatening (confirmed as unstable angina by the CEC). The only SAE in the treatment period which was considered to be drug-related by the investigator was a case of worsening of pre-existing bronchial hyperreactivity (linagliptin).

Protocol-defined significant AEs were assessed via a combination of 'standard MedDRA (medical drug dictionary for drug regulatory affairs) queries' and investigator reporting to evaluate hypersensitivity reactions, liver toxicity, and acute renal failure. These AEs were reported for 4 patients (2.3%) in the placebo group (1 patient with hypersensitivity, 1 patient with renal impairment, 1 patient with increased AST and ALT, and 1 patient with increased ALT) and 3 patients (0.6%) in the linagliptin group (2 patients with increased ALT and AST values and 1 patient with worsening of pre-existing bronchial hyperreactivity).

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'Other significant' AEs (as defined by the ICH E3 guideline) were reported for 1 patient (0.6%) in the placebo group (constipation and diarrhoea) and 10 patients (1.9%) in the linagliptin group (paronychia, upper respiratory tract infection, urinary tract infection, hyperglycaemia, diabetic neuropathy, anxiety, temporal arteritis, hepatic steatosis, skin ulcer and increased blood glucose).

Laboratory parameters

Overall, the safety laboratory data revealed no trends of clinical relevance. Mean values of amylase were observed to be slightly higher at the end of treatment for both treatment groups (mean increase of 4 U/L [SD 22] for placebo and 5 U/L [SD 20] for linagliptin with respect to baseline), with transitions to high values with respect to baseline relative to the normal reference range observed in 6.4% of the patients in the placebo group and 5.9% of the patients in the linagliptin group.

With regard to lipids, mean values for total cholesterol, high-density lipoproteins (HDL), and low-density lipoproteins (LDL) were within the normal reference range at baseline and end of treatment for both treatment groups, with small mean changes from baseline (cholesterol: 4 mg/dL [SD 16] placebo, 1 mg/dL [SD 12] linagliptin; HDL: 1 mg/dL [SD 9] placebo, 1 mg/dL [SD 7] linagliptin; and LDL: 9 mg/dL [SD 23] placebo, 4 mg/dL [SD 22] linagliptin). Triglyceride mean values were above the normal reference range both at baseline and end of treatment for both treatment groups, with mean changes from baseline of −7 mg/dL (SD 183) in the placebo group and −21 mg/dL (SD 148) in the linagliptin group.

Proportions of patients with possibly clinically significant laboratory abnormalities (PCSAs) reported were comparable between treatment groups, with slight numerical differences in the proportions of patients with increased values for haemoglobin (2.3% placebo;0.8% linagliptin), amylase (3.5% placebo; 2.0% linagliptin), and triglycerides (12.7% placebo; 8.5% linagliptin). Possibly clinically significant increased AST values were recorded for 1 patient (0.6%) in the placebo group with 236 U/L (>6 x ULN), and 1 patient (0.2%) in the linagliptin group with 170 U/L (>4 x ULN). With regard to ALT, a possibly clinically significant increase was recorded for 2 patients (1.2%) in the placebo group (highest value: 518 U/L [>11 x ULN],) and 1 patient (0.2%) in the linagliptin group (204 U/L [>4 x ULN]. For 2 of these patients, 1 patient in each

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treatment group, the increased transaminase values were considered significant AEs, and additionally led to treatment discontinuation. One patient (0.6%) in the placebo group had a decreased glucose value of 47 mg/dL (reported as a hypoglycaemic event); this patient had been receiving a sulfonylurea as rescue medication.

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. Overall, based on MDRD (modification of diet in renal disease) and eCCr renal (estimated creatinine clearance rate, Cockcroft-Gault formula) staging, the vast majority of patients (over 95%) remained within normal renal function (stage 1) or mild renal impairment (stage 2). In general there were only minor shifts in function staging. In the placebo group, 3.0% of patients moderate renal impairment (stage 3) at baseline versus 2.4% at the end of treatment. In the linagliptin group, 3.5% of patients had moderate renal impairment at baseline versus 3.1% of patients at the end of treatment. One patient (0.2%) in the linagliptin group, with moderate renal impairment at baseline, shifted to severe renal impairment (stage 4/5) at the end of the trial.

Vital signs

There were no relevant trends observed over time in the mean changes from baseline for blood pressure or pulse rate in either of the treatment groups. Across the visits, systolic blood pressure mean changes from baseline ranged from −0.34 to 1.64 mmHg in the placebo group and from −1.84 mmHg to −0.27 mmHg in the linagliptin group. Diastolic blood pressure mean changes from baseline ranged from −0.73 mmHg to 0.73 mmHg in the placebo group and from −1.26 mmHg to −0.32 mmHg in the linagliptin group.

Conclusions:

Treatment with 5 mg linagliptin once daily was superior to placebo in the reduction of HbA_{1c} and fasting plasma glucose levels, as add-on therapy in patients with type 2 diabetes mellitus and insufficient glycaemic control on metformin monotherapy alone. Linagliptin was efficacious and generally well-tolerated. The assessment of safety did not reveal any major trends of clinical relevance. Few cases of hypoglycaemia were reported in this trial, with a numerically lower incidence observed on treatment with linagliptin and metformin than on treatment with placebo and metformin.