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ORIGINAL ARTICLE

# Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study

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**Aim:** To evaluate the efficacy and safety of the potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin administered as add-on therapy to metformin in patients with type 2 diabetes with inadequate glycaemic control.

**Methods:** This 24-week, randomized, placebo-controlled, double-blind, parallel-group study was carried out in 82 centres in 10 countries. Patients with HbA1c levels of 7.0–10.0% on metformin and a maximum of one additional antidiabetes medication, which was discontinued at screening, continued on metformin ≥1500 mg/day for 6 weeks, including a placebo run-in period of 2 weeks, before being randomized to linagliptin 5 mg once daily (n = 524) or placebo (n = 177) add-on. The primary outcome was the change from baseline in HbA1c after 24 weeks of treatment, evaluated with an analysis of covariance (ANCOVA).

**Results:** Mean baseline HbA1c and fasting plasma glucose (FPG) were 8.1% and 9.4 mmol/l, respectively. Linagliptin showed significant reductions vs. placebo in adjusted mean changes from baseline of HbA1c (−0.49 vs. 0.15%), FPG (−0.59 vs. 0.58 mmol/l) and 2hPPG (−2.7 vs. 1.0 mmol/l); all $p < 0.0001$. Hypoglycaemia was rare, occurring in three patients (0.6%) treated with linagliptin and five patients (2.8%) in the placebo group. Body weight did not change significantly from baseline in both groups (−0.5 kg placebo, −0.4 kg linagliptin).

**Conclusions:** The addition of linagliptin 5 mg once daily in patients with type 2 diabetes inadequately controlled on metformin resulted in a significant and clinically meaningful improvement in glycaemic control without weight gain or increased risk of hypoglycaemia.

**Keywords:** combination therapy, dipeptidyl peptidase-4, DPP-IV inhibitor, glycaemic control, linagliptin, metformin, metformin add-on, type 2 diabetes

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## Introduction

Diabetes affects an estimated 285 million adults worldwide and causes approximately four million deaths each year [1,2]. Management strategies in type 2 diabetes aim to achieve and maintain glycaemic control to HbA1c levels of <6.5% [3] or <7.0% [4] to reduce the risk of complications. However, despite treatment with lifestyle changes and effective oral hypoglycaemic monotherapy, the progressive decline in glucose control persists, eventually necessitating combination therapy for many patients [5,6].

The dipeptidyl peptidase-4 (DPP-4) inhibitors are a promising class of drugs for the treatment of type 2 diabetes. These act by delaying the breakdown of endogenous incretin peptides such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These intestinal peptides, secreted in response to food intake, are essential in postprandial glucose homeostasis as they enhance insulin secretion in a glucose-dependent fashion and consequently lower plasma glucose [7–11]. GLP-1 also lowers the inappropriately elevated postprandial glucagon secretion and reduces gastric emptying. Overall, these dual actions modulated by incretin peptides result in improved glycaemic control [9,10,12]. As incretin enhancers, the DPP-4 inhibitor class may be particularly useful when used early in the course of the disease and could have the potential to preserve $\beta$-cell function and therefore maintain glycaemic control over time [6,8,10,13].

Linagliptin is a novel, xanthine-based DPP-4 inhibitor which has a predominantly non-renal route of excretion. This potent and selective agent inhibits DPP-4 with an IC50 of ~1 nM and has a particularly long duration of action (>80% DPP-4 inhibition at 24-h postdose), both of which are factors that allow for convenient once-daily dosing [14–16]. It is excreted primarily unchanged via the faeces, so it is not expected to

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require dose adjustment in patients with renal insufficiency as is required with other DPP-4 inhibitors [10,15–20]. Linagliptin has been shown to be well tolerated at doses greater than 100-fold in excess of the therapeutic dose of 5 mg, so has a larger safety margin [15]. Animal and early clinical studies have recorded an approximate threefold increase in the level of circulating GLP-1 following treatment with linagliptin [16,21]. Furthermore, in phase II clinical trials, linagliptin significantly improved glycaemic control, reducing glucose excursions following an oral glucose tolerance test and showed an excellent tolerability and safety profile with an adverse event incidence comparable to that of placebo [15,16,22,23].

Following these favourable initial findings, research interest has turned to further assess the combination of linagliptin with metformin, the most commonly prescribed first-line treatment for diabetes, and considered to be the first choice in the management of type 2 diabetes [24,25]. Metformin acts by improving insulin sensitivity and decreasing hepatic glucose production, so co-administration of linagliptin in individuals with inadequate glycaemic control with metformin alone would be pharmacologically sound and intuitive because of the complementary mechanisms of action of these two agents [13,25]. The effect of inhibiting DPP-4 is to increase exposure to GLP-1, resulting in the lowering of circulating glucose through enhanced insulin secretion and inhibition of glucagon secretion [26]. This is believed to complement the suppression of hepatic glucose production and improved insulin sensitivity associated with metformin [27]. Furthermore, the lack of clinically relevant pharmacokinetic interactions of these medications and their corresponding weight-neutral effects also support this combination [13,25].

The objective of this phase III study was to investigate the efficacy and safety of linagliptin 5 mg vs. placebo administered for 24 weeks as add-on therapy to metformin in patients with type 2 diabetes having insufficient glycaemic control.

## Methods

### Study Design

This randomized, double-blind, placebo-controlled, parallel-group study was carried out in 82 centres in 10 countries (Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden and United States). It comprised a 2-week run-in with or without a prior 4-week washout period, followed by 24 weeks of double-blind treatment and a 1-week follow-up period.

### Study Population

Male and female patients aged 18–80 years, previously diagnosed with type 2 diabetes and a body mass index (BMI) $\leq$40 kg/m$^2$, were included. Subjects needed to be receiving metformin at a dose of $\geq$1500 mg/day (or maximum tolerated dose) and not more than one other oral antidiabetes medication. The antidiabetes medication(s) must have remained unchanged for 10 weeks prior to the date of informed consent and the dose of metformin stable for $\geq$12 weeks before randomization. At screening, the HbA1c inclusion threshold was 7.0–10.0% for patients who had previously been treated with metformin monotherapy (approximately two-thirds of patients) or 6.5–9.0% for those who had also been treated with an additional medication. By the start of the placebo run-in, the HbA1c requirement was 7.0–10.0% for all patients.

Patients were excluded if they had been treated with rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, had changed their dosage of thyroid hormone treatment within 6 weeks or were being treated with systemic steroids at the date of informed consent. Patients were excluded if they had impaired hepatic function [serum levels of either alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase (ALP) more than three times the upper limit of normal], renal failure or renal impairment (serum creatinine $\geq$135 μmol/l) or had suffered myocardial infarction, stroke or transient ischaemic attack within 6 months of giving informed consent. Other exclusion criteria included a history of acute or chronic metabolic acidosis, unstable or acute congestive heart failure, hereditary galactose intolerance or dehydration. Patients could not have participated in another trial of an investigational drug within the previous 2 months.

The trial was carried out according to the Declaration of Helsinki and good clinical practice principles. The protocol was approved by all relevant local independent ethical review or institutional review committees. All patients provided written informed consent before participation.

### Study Procedures

Patients taking an antidiabetes medication in addition to metformin stopped this medication and underwent a 6-week washout period which included an open-label placebo run-in phase in the last 2 weeks. For patients taking only metformin at enrolment, only the 2-week placebo run-in was required. Eligible patients were then randomized to double-blind treatment with either placebo or linagliptin 5 mg once daily orally for 24 weeks. All patients continued to take their usual dosage of metformin throughout all phases of the trial.

Randomization was in a 3 : 1 ratio to linagliptin or placebo. This allocation was stratified by the level of glycaemic control at the start of the placebo run-in (HbA1c $<$8.5% or $\geq$8.5%) and according to the use of monotherapy vs. combination therapy at enrolment.

Eight study visits were scheduled: at screening, at the start of the placebo run-in, weeks 0, 6, 12, 18 and 24 and at the week 25 follow-up. Patients previously receiving combination antidiabetes therapy were seen at an additional visit at the start of their washout period. All patients were provided with, and trained in the correct use of, home blood glucose monitoring (HBGM) equipment. In addition, all patients received dietary counselling.

Rescue medication (sulphonylurea) could be initiated during the randomized period only (i.e. between visit 3 and visit 7). During the first 12 weeks of randomized treatment, rescue medication was to be initiated only if a patient had a confirmed glucose level $>$13.3 mmol/l after an overnight fast. During the last 12 weeks of randomized treatment, rescue medication was to be initiated only if a patient had a confirmed glucose level of 11.1 mmol/l after an overnight fast or of $>$22.2 mmol/l in

a randomly performed measurement. Patients receiving rescue therapy remained in the trial and were not unblinded.

HbA1c, fasting plasma glucose (FPG), adverse events (AEs), serious adverse events (SAEs) and vital signs were evaluated at every visit. Body weight was recorded and a 12-lead electrocardiogram (ECG) carried out at screening and weeks 0 and 24. Also at these time points, measurements of insulin and C-peptide were made and a meal tolerance test was undertaken in a subset of patients to assess 2-h postprandial glucose (2hPPG) levels. The meal tolerance test at week 24 was taken 30 min after linagliptin dosing. Safety assessments were made at screening, placebo run-in and weeks 0, 12, 24 and 25. Routine laboratory analyses and HbA1c determinations were carried out by a central laboratory. Plasma glucose, insulin and C-peptide levels were evaluated by MDS Pharma Services, France.

### Study Outcomes

The primary endpoint of this study was the change from baseline in HbA1c after 24 weeks of treatment. The main secondary endpoints were the change from baseline in FPG and 2hPPG after 24 weeks of treatment, the change from baseline in HbA1c and FPG over time, the percentage of patients achieving an HbA1c on treatment $<7.0\%$ and $<6.5\%$, and the percentage of patients achieving an HbA1c lowering of $\geq 0.5\%$. Other endpoints included the proportion of patients requiring rescue medication, the change from baseline in body weight and the change in biomarkers of insulin sensitivity, $\beta$-cell function and of postprandial glucose control.

Safety evaluation criteria included the incidence and intensity of AEs, withdrawals because of AEs, physical examination, 12-lead ECG, vital signs and clinical laboratory parameters.

### Statistical Analysis

A sample size of 600 patients (450 linagliptin and 150 placebo) was required to ensure 95% power to detect a 0.6% treatment difference in this study, assuming a standard deviation of 1.6% for the difference in HbA1c from baseline.

The primary endpoint, the change from baseline in HbA1c after 24 weeks of treatment, was compared between linagliptin and placebo groups using an analysis of covariance (ANCOVA) with the fixed factors 'treatment' as well as 'wash-out' and 'HbA1c baseline' as linear covariate. This analysis was performed on the full analysis set (FAS) with the last observation carried forward (LOCF) to impute missing values. This group comprised all randomized patients who were treated with at least one dose of study medication, had a baseline HbA1c measurement and had at least one on-treatment HbA1c measurement. The impact of all methods of handling missing data was analysed by means of a sensitivity analysis.

ANCOVA and logistic regression techniques were applied to assess all continuous and categorical secondary and safety endpoints, respectively. Kaplan–Meier curves were conducted in addition to evaluate the use of rescue medication. Descriptive statistics were used predominantly. No missing values were imputed for safety evaluations or biomarkers.

This study is registered with ClinicalTrials.gov, number NCT00601 250.

## Results

### Demographics and Baseline Characteristics

A total of 1268 patients were enroled and 701 randomized to treatment (524 to linagliptin, 177 to placebo) (figure 1). One patient randomized to the linagliptin group withdrew consent for the study and therefore did not receive treatment. The baseline characteristics were similar between the groups including the level of glycaemic control (Table 1). Approximately two-thirds of patients had previously been treated with metformin monotherapy.

### Efficacy and Biomarkers

Linagliptin was significantly better than placebo at reducing the adjusted mean HbA1c from a mean baseline of 8.1% (Table 2). After 24 weeks of treatment, linagliptin reduced the mean HbA1c level by 0.49%, whereas in the placebo group HbA1c rose by 0.15%, equating to a treatment difference of $-0.64\%$ (95% CI $-0.78$ to $-0.50$; $p < 0.0001$). The significant difference between treatments in mean HbA1c change increased over time from 6 weeks ($-0.43\%$) to 18 weeks ($-0.65\%$) and then remained stable until the end of the 24 weeks ($-0.64\%$) (figure 2). Figure 3a, b shows the reduction in HbA1c from baseline over time for the subgroups of patients who underwent washout and those who did not. The placebo-corrected reduction in HbA1c from baseline at 24 weeks was greater in patients who had previously been treated with one oral antidiabetic drug (OAD) in addition to metformin compared with patients who did not require a washout period, having only received metformin ($-0.79$ vs. $-0.60\%$, respectively, but this was not significant).

Among patients with a baseline HbA1c of $\geq 7.0\%$, 26% of individuals treated with linagliptin vs. 9% of those in the placebo group achieved the HbA1c target of $<7.0\%$ at 24 weeks. Among this subgroup, patients treated with linagliptin were significantly more probable to reach the target of an HbA1c of $<7.0\%$ than were patients in the control group (odds ratio 4·4, 95% CI 2.4, 8.0; $p = 0.0001$). A significant difference was also seen with regard to reaching a target of $<6.5\%$ for those with a baseline HbA1c of $\geq 6.5\%$ [10% with linagliptin vs. 2% with placebo (odds ratio 5.5, 95% CI 1.9, 15.6; $p = 0.0016$)]. Similarly, 50% of those treated with linagliptin compared with 22% of the placebo group achieved a reduction in HbA1c of $\geq 0.5\%$ at 24 weeks (odds ratio 3.8, 95% CI 2.5, 5.7; $p < 0.0001$).

The mean change from baseline in FPG over time was analysed and a similar pattern was seen as for HbA1c, with levels in the linagliptin-treated patients decreasing over time, while those in the placebo group increased over time (figure 4). The difference between treatments in terms of adjusted mean change from baseline in FPG increased over time ($-0.9$ mmol/l to $-1.2$ mmol/l with all p-values $<0.0001$). As with HbA1c, the placebo-corrected change from baseline in FPG at 24 weeks was greater in patients who had previously been treated with one OAD plus metformin compared with patients who did not require a washout period ($-1.57$ vs. $-1.18$ mmol/l, respectively, not significant).

Linagliptin led to a significant reduction vs. placebo in adjusted mean FPG levels ($-0.6$ vs. 0.6 mmol/l, respectively)

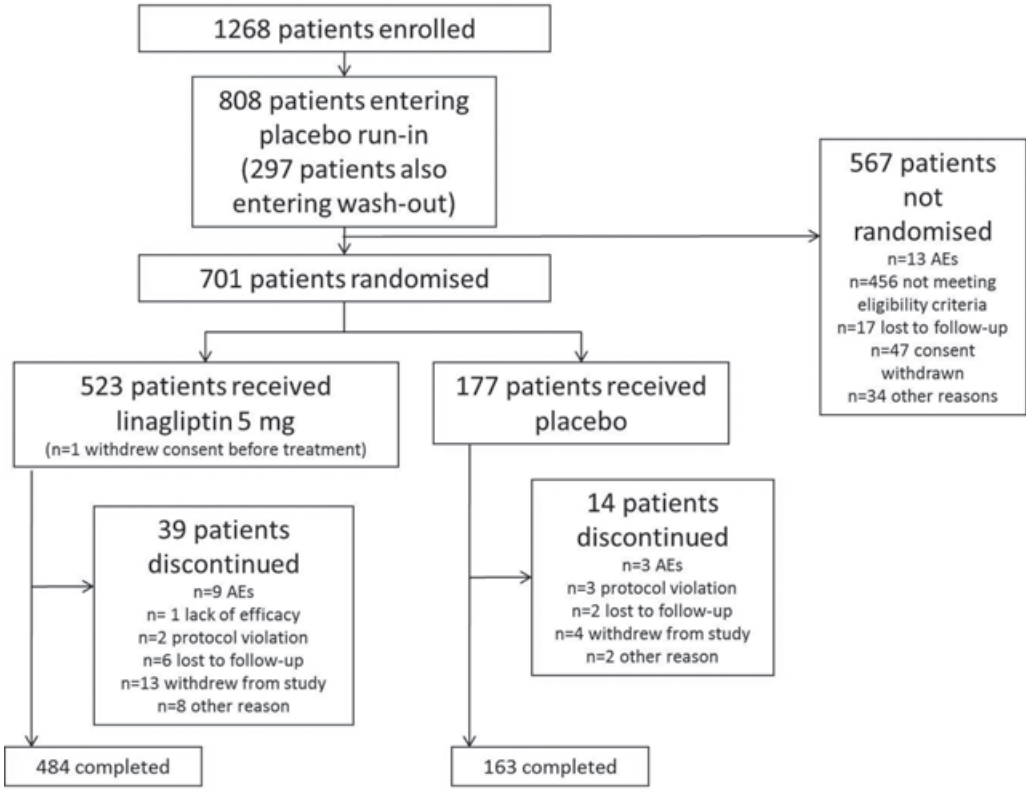


**Figure 1.** Flow diagram of patient disposition.

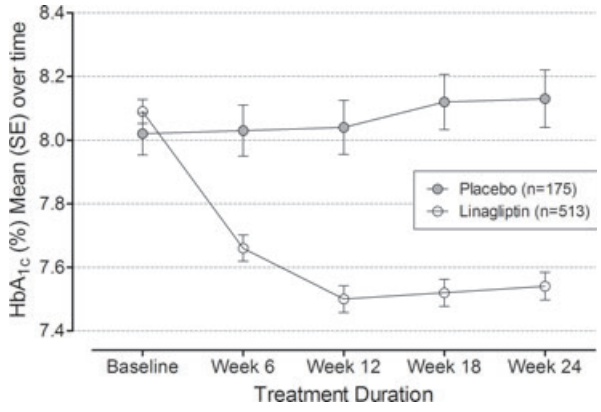


**Figure 2.** Change over time (mean ± standard error) in HbA1c following treatment with linagliptin 5 mg or placebo for 24 weeks—FAS (LOCF). Differences in change from baseline in HbA11c between placebo and linagliptin were significant at each time point after baseline ($p < 0.0001$). FAS, full analysis set; LOCF, last observation carried forward.

representing a treatment effect of −1.2 mmol/l; $p < 0.0001$ (Table 2). Similarly, linagliptin showed a significant treatment effect in controlling postprandial glucose levels. From baseline to week 24, the adjusted mean 2hPPG level fell by 2.7 mmol/l, compared with an increase of 1.0 mmol/l in the placebo group. This translated to a difference of −3.7 mmol/l ($p < 0.0001$) between the two groups, favouring linagliptin treatment. The adjusted mean change from baseline in 2hPPG at week 24 is shown in figure 5.

With regard to the meal tolerance test parameters, total glucose AUC showed a significant effect with linagliptin. Adjusted mean total glucose AUC increased by 1.6 mmol*h/l in the placebo group and decreased by 3.8 mmol*h/l in the treatment group, creating a treatment difference of −5.4 mmol*h/l ($p < 0.0001$) from baseline to week 24. The disposition index also suggested an improvement in $\beta$-cell function after linagliptin treatment, although this change did not reach statistical significance.

The assessment of biomarkers and derived indices revealed a significant treatment effect for linagliptin in adjusted mean change from baseline in fasting C-peptide levels at 24 weeks (mean difference of −134.4 pmol/l; $p = 0.031$). Homeostasis model assessment of $\beta$-cell function/insulin secretion (HOMA-%B) also showed a clinically relevant difference between the treatment groups in adjusted mean change from baseline at 24 weeks of 11.9 (mU/l)/(mmol/l)—relative change of 1.26 (mU/l)/(mmol/l) ($p = 0.0005$; log-transformed data only). The analysis on the basis of the non-transformed data is summarized in Table 2.

Subgroup analysis by baseline HbA1c of adjusted mean changes in HbA1c from baseline showed a greater reduction in patients with a higher baseline HbA1c. Figure 6 shows the adjusted mean change from baseline HbA1c stratified by baseline HbA1c. Linagliptin patients with a baseline HbA1c level of ≥9.0% showed a greater reduction in HbA1c than the overall cohort (−0.95%; 95% CI −1.12, −0.78) compared with placebo (−0.23%; 95% CI −0.54, 0.07; $p < 0.0001$).

**Table 1.** Demographic and baseline characteristics.

| | Placebo (n = 177) | Linagliptin (n = 523) | Total (n = 700) |
|---|---|---|---|
| Male gender [n (%)] | 101 (57) | 278 (53) | 379 (54) |
| Age (years) | 56.6 ± 10.9 | 56.5 ± 10.1 | 56.5 ± 10.3 |
| Race [n (%)] | | | |
| White | 140 (79) | 393 (75) | 533 (76) |
| Asian | 32 (18) | 114 (22) | 146 (21) |
| Others | 5 (3) | 16 (3) | 21 (3) |
| Weight (kg) | 83.3 ± 16.6 | 82.2 ± 17.2 | 82.5 ± 17.1 |
| Body mass index (kg/m$^2$) | 30.05 ± 5.01 | 29.85 ± 4.84 | 29.90 ± 4.88 |
| HbA1c (%) | 8.02 ± 0.88 | 8.09 ± 0.86 | 8.08 ± 0.87 |
| FPG (mmol/l) | 9.2 ± 2.3 | 9.4 ± 2.4 | 9.4 ± 2.4 |
| eGFR (ml/min/1.73m$^2$) | | | |
| ≥90 | 112 ± 63.3 | 302 ± 57.7 | 414 ± 59.1 |
| 60 to <90 | 55 ± 31.1 | 183 ± 35.0 | 238 ± 34.0 |
| 30 to <60 | 5 ± 2.8 | 18 ± 3.4 | 23 ± 3.3 |
| Missing | 5 ± 2.8 | 20 ± 3.8 | 25 ± 3.6 |
| eCCR ≥80 ml/min [n (%)] | 148 (84) | 423 (81) | 571 (82) |
| Previous antidiabetes drugs [n (%)] | | | |
| Metformin only | 121 (69) | 351 (68) | 472 (69) |
| Metformin plus one other | 54 (31) | 162 (32) | 216 (31) |
| Time since diagnosis [n (%)] | | | |
| ≤1 year | 22 (13) | 54 (11) | 76 (11) |
| >1–5 years | 60 (34) | 174 (34) | 234 (34) |
| >5 years | 93 (53) | 285 (56) | 378 (55) |
| Analysis sets | | | |
| Treated [n] | 177 | 523 | 700 |
| FAS [n (% of treated set)] | 175 (99) | 513 (98) | 688 (98) |
| FAS-completers [n (% of FAS)] | 156 (89) | 468 (91) | 624 (91) |
| PPS [n (% of FAS)] | 156 (89) | 460 (90) | 616 (90) |
| MTT [n (% of FAS)] | 26 (15) | 86 (17) | 111 (16) |

Data are mean ± standard deviation unless otherwise stated. FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; eCCR, estimated creatinine clearance rate; FAS, full analysis set (i.e. patients who had a baseline and at least one on-treatment HbA1c measurement), FAS-completers (i.e. all patients completing 24 weeks treatment and with HbA1c measurement at week 24); PPS, per protocol set (i.e. patients in FAS with no important protocol violations); MTT, meal tolerance test (i.e. subgroup of patients in FAS with a valid MTT at baseline and visit 7).

More than twice as many patients in the placebo group compared with those receiving linagliptin required rescue medication (19 vs. 8%, respectively, associated odds ratio 0.28, p = 0.0001). Finally, neither group was associated with any significant change in mean body weight from baseline to week 24 (−0.5 kg placebo; −0.4 kg linagliptin).

### Tolerability and Safety

Overall, linagliptin was well tolerated and the safety assessment revealed no trends of clinical relevance. AEs occurred at a similar rate in both groups (Table 3). Most were mild or moderate in intensity with only 2 and 1% of patients treated with linagliptin or placebo, respectively, reporting AEs of severe intensity. All hypoglycaemic events (plasma glucose concentration ≤3.9 mmol/l) were of mild intensity and assistance was not required by any patient. In the linagliptin group, all three hypoglycaemic events were asymptomatic and only two were considered drug-related. All events occurred in the absence of rescue medication. In the placebo group, two of the five events were asymptomatic and four patients had been receiving rescue medication (sulphonylurea) at the time of onset.

The proportion of treatment-related AEs was slightly higher among patients in the placebo group (10.7%) than with linagliptin (6.9%) as add-on to metformin. This was mostly because of hyperglycaemia which was more common in the placebo group (2.3 vs. 1.0% in the linagliptin group) and hypoglycaemia (2.3 vs. 0.4%, respectively).

Three patients (1.7%) in the placebo group and eight patients (1.5%) in the linagliptin group reported AEs leading to discontinuation. Overall, SAEs were reported for 18 patients receiving linagliptin (3.4%) and four patients receiving placebo (2.3%). The analyses of laboratory variables and vital signs did not reveal any clinically significant findings. No relevant trends were observed in the mean changes from baseline for blood pressure or pulse rate in either of the study groups.

## Discussion

This study shows that, for patients inadequately controlled on metformin alone, the addition of linagliptin 5 mg once daily over 24 weeks brings a significant and clinically meaningful improvement in glycaemic control, evident in measures of pre- and postprandial plasma glucose as well as HbA1c. In particular, linagliptin improved postprandial glucose levels, whereas there was a marked deterioration on placebo. The changes in FPG and 2hPPG (as percentage mean treatment effect) were 12%

**Table 2.** Glycaemic efficacy and change in other parameters.

| Parameter | n | Baseline | Adjusted mean change from baseline | Adjusted mean treatment effect (95% CI; p value) |
|---|---|---|---|---|
| *Glycaemic control* | | | | |
| HbA1c (%)* | | | | |
| Placebo | 175 | 8.02 ± 0.07 | 0.15 ± 0.06 | −0.64 ± 0.07 |
| Linagliptin | 513 | 8.09 ± 0.04 | −0.49 ± 0.04 | (−0.78 to −0.50; p < 0.0001) |
| FPG (mmol/l)* | | | | |
| Placebo | 159 | 9.1 ± 0.2 | 0.6 ± 0.2 | −1.2 ± 0.2 |
| Linagliptin | 495 | 9.4 ± 0.1 | −0.6 ± 0.1 | (−1.5 to −0.8; p < 0.0001) |
| 2hPPG (mmol/l) | | | | |
| Placebo | 21 | 15.2 ± 0.8 | 1.0 ± 0.7 | −3.7 ± 0.8 |
| Linagliptin | 78 | 15.0 ± 0.4 | −2.7 ± 0.4 | (−5.3 to −2.2; p < 0.0001) |
| *Biomarkers of insulin sensitivity/β-cell function* | | | | |
| C-peptide (pmol/l) | | | | |
| Placebo | 34 | 1069.7 ± 67.9 | 70.3 ± 55.4 | −134.4 ± 61.7 |
| Linagliptin | 104 | 965.8 ± 45.2 | −64.1 ± 34.0 | (−256.4 to −12.4; p = 0.031) |
| Insulin (mU/l) | | | | |
| Placebo | 102 | 11.0 ± 0.8 | −2.5 ± 0.7 | 0.9 ± 0.8 |
| Linagliptin | 336 | 11.8 ± 0.7 | −1.6 ± 0.4 | (−0.7 to 2.5; p = 0.26) |
| HOMA-IR [(mU/l) × (mmol/l)] | | | | |
| Placebo | 98 | 4.5 ± 0.4 | −1.0 ± 0.3 | −0.0 ± 0.3 |
| Linagliptin | 323 | 4.9 ± 0.4 | −1.0 ± 0.2 | (−0.7 to 0.7; p = 0.99) |
| HOMA-%B [(mU/l)/(mmol/l)] | | | | |
| Placebo | 98 | 48.3 ± 4.8 | −10.7 ± 6.9 | 11.9 ± 7.6 |
| Linagliptin | 323 | 49.7 ± 3.6 | 1.2 ± 3.9 | (−3.0 to 26.8; p = 0.12) |
| Disposition index [1/((mmol/l) × (mmol/l))] | | | | |
| Placebo | 120 | 12.7 ± 0.9 | 1.4 ± 5.0 | 4.5 ± 5.4 |
| Linagliptin | 394 | 12.8 ± 0.9 | 5.9 ± 2.8 | (−6.1 to 15.1; p = 0.41) |
| *Meal tolerance test* | | | | |
| Total glucose AUC (mmol*h/l) | | | | |
| Placebo | 21 | 28.0 ± 1.3 | 1.6 ± 1.1 | −5.4 ± 1.2 |
| Linagliptin | 77 | 26.3 ± 0.6 | −3.8 ± 0.6 | (−7.7 to −3.0; p < 0.0001) |
| Total insulin AUC (mU*h/l) | | | | |
| Placebo | 13 | 457.1 ± 90.6 | 104.7 ± 79.2 | −19.6 ± 88.8 |
| Linagliptin | 46 | 511.9 ± 44.9 | 85.1 ± 49.5 | (−197.6 to 158.5; p = 0.83) |
| Total C-peptide AUC (pmol*h/l) | | | | |
| Placebo | 14 | 3369.1 ± 391.4 | 906.5 ± 314.3 | −342.7 ± 351.3 |
| Linagliptin | 57 | 3473.6 ± 175.0 | 563.8 ± 181.7 | (−1044 to 358.7; p = 0.33) |
| Total insulin AUC/total glucose AUC ratio | | | | |
| Placebo | 13 | 18.4 ± 3.6 | 3.9 ± 3.2 | 2.1 ± 3.6 |
| Linagliptin | 45 | 21.0 ± 1.9 | 6.0 ± 2.0 | (−5.2 to 9.4; p = 0.56) |
| Total insulin AUC/total C-peptide AUC ratio | | | | |
| Placebo | 11 | 0.12 ± 0.01 | 0.01 ± 0.01 | −0.01 ± 0.01 |
| Linagliptin | 40 | 0.14 ± 0.01 | −0.01 ± 0.01 | (−0.04 to 0.01; p = 0.29) |
| Total glucose AUC/(total insulin AUC/total C-peptide AUC ratio) | | | | |
| Placebo | 11 | 254.4 ± 33.0 | 4.4 ± 29.6 | −47.5 ± 33.2 |
| Linagliptin | 39 | 219.1 ± 25.3 | −43.0 ± 18.1 | (−114.3 to 19.4; p = 0.16) |

Data are means ± standard error or mean (95% CI).
*Last observation carried forward, others are observed cases.

and 25%, respectively. The latter is of particular interest as the postprandial state in patients with type 2 diabetes is associated with endothelial dysfunction and therefore risk of cardiovascular complications [28]. The trial also provides further evidence of tolerability comparable to placebo, low incidence of acute hypoglycaemic events and weight-neutral effect of linagliptin.

Adding linagliptin to metformin monotherapy in this trial led to a clinically meaningful placebo-corrected reduction of 0.64% in HbA1c, 1.2 mmol/l in FPG and 3.7 mmol/l in 2hPPG concentrations, and a significant increase in the likelihood of achieving an HbA1c target of <7.0% after 24 weeks of treatment. These results confirm a previous 12-week study of linagliptin added to metformin in 333 patients with uncontrolled diabetes in which a significant placebo-subtracted reduction of 0.73% in HbA1c was achieved, with up to 21% of treated patients reaching HbA1c targets of <7% [23,29]. Although true comparisons of the efficacy of

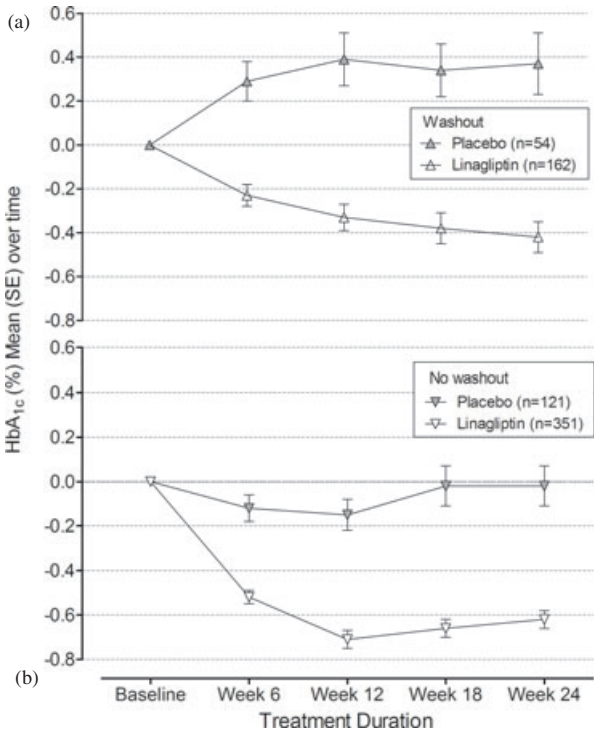


**Figure 3.** (a) Mean change from baseline in HbA1c following treatment with linagliptin 5 mg or placebo for 24 weeks for patients who had been treated with one OAD in addition to metformin and underwent washout—FAS (LOCF). (b) Mean change from baseline in HbA1c following treatment with linagliptin 5 mg or placebo for 24 weeks for patients who were treated only with metformin and did not require washout—FAS (LOCF). FAS, full analysis set; LOCF, last observation carried forward.

different medications necessitate head-to-head clinical trials, the clinically relevant reductions in HbA1c associated with linagliptin, like others in its class, are therefore generally comparable to those of other glucose-lowering drugs, but associated with better tolerability [7,11,23,29–33].

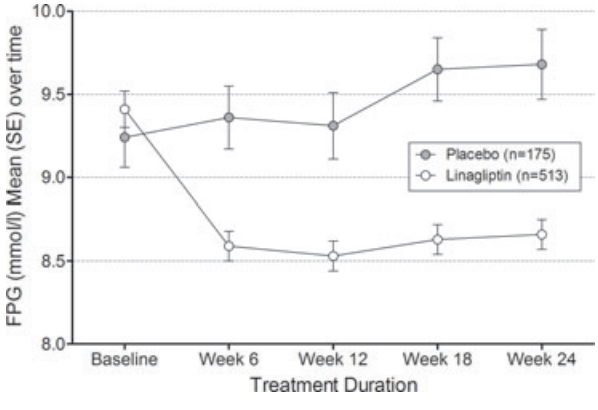


**Figure 4.** Change over time (mean ± s.e.) in FPG following treatment with linagliptin 5 mg or placebo for 24 weeks—FAS (LOCF). Differences in change from baseline in FPG between placebo and linagliptin were significant at each time point after baseline ($p < 0.0001$). FAS, full analysis set; LOCF, last observation carried forward.

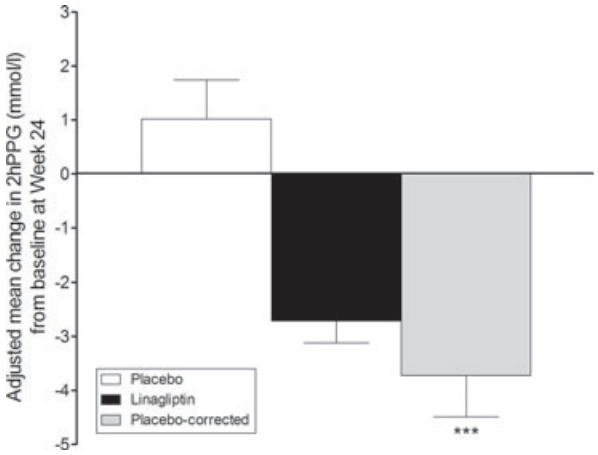


**Figure 5.** Adjusted mean change in 2-h postprandial glucose (2hPPG) from baseline following treatment with linagliptin 5 mg or placebo for 24 weeks as add-on therapy to metformin (MTT set) (***$p < 0.0001$).

Additionally, in the present study there was a trend for improvement in measures of $\beta$-cell function. In particular, fasting C-peptide concentration was significantly lower in the linagliptin-treated patients than in the placebo group and the log-transformed mean change from baseline in HOMA-%B at 24 weeks also reached significance. These data add to a growing body of evidence that linagliptin 5 mg once daily is an effective and well-tolerated treatment for type 2 diabetes [13–15]. Linagliptin enhanced markers of $\beta$-cell function—HOMA-%B and 2hPPG concentration, consistent with an increased availability of endogenous GLP-1, which stimulates the proliferation and differentiation of pancreatic $\beta$-cells. This is an area requiring further research, since assumptions are based on animal studies and biomarkers. However, if suggestions of a $\beta$-cell protective effect for DPP-4 inhibitors can be borne out, this class may establish a role in early disease management [8,10].

In this study linagliptin had an overall side effect profile similar to placebo. Of particular note is the low propensity of linagliptin to cause acute hypoglycaemic events. This is an

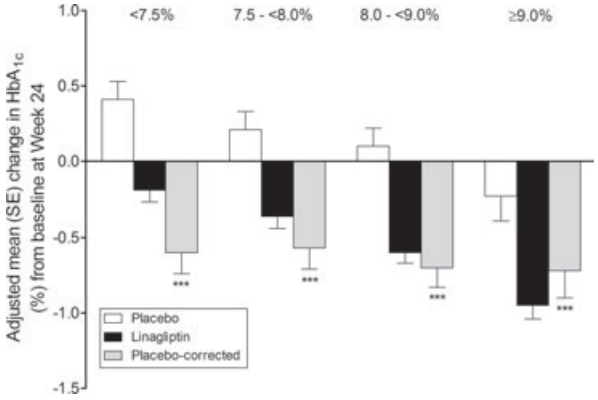


**Figure 6.** Adjusted mean change in HbA1c over time by subgroup following treatment with linagliptin 5 mg or placebo for 24 weeks as add-on therapy to metformin [FAS (LOCF)] (***$p < 0.0001$). FAS, full analysis set; LOCF, last observation carried forward.

**Table 3.** Summary of adverse events by preferred term.

| | Placebo (n = 177) | Linagliptin (n = 523) |
|---|---|---|
| Incidence of AEs | | |
| Any AE | 98 (55.4) | 276 (52.8) |
| Severe | 2 (1.1) | 11 (2.1) |
| Drug-related AE | 19 (10.7) | 36 (6.9) |
| AEs leading to discontinuation | 3 (1.7) | 8 (1.5) |
| Significant AEs* | 4 (2.3) | 2 (0.4) |
| SAEs | 4 (2.3) | 18 (3.4) |
| Most frequent AEs (occurring in >2% patients) | | |
| Hyperglycaemia | 26 (14.7) | 27 (5.2) |
| Nasopharyngitis | 9 (5.1) | 27 (5.2) |
| Influenza | 5 (2.8) | 18 (3.4) |
| Hypertension | 6 (3.4) | 17 (3.3) |
| Urinary tract infection | 7 (4.0) | 16 (3.1) |
| Headache | 7 (4.0) | 15 (2.9) |
| Upper respiratory tract infection | 4 (2.3) | 15 (2.9) |
| Diarrhoea | 4 (2.3) | 15 (2.9) |
| Back pain | 5 (2.8) | 12 (2.3) |
| Arthralgia | 3 (1.7) | 11 (2.1) |
| Blood glucose increased | 7 (4.0) | 5 (1.0) |
| Hypoglycaemia† | 5 (2.8) | 3 (0.6) |
| Abdominal pain | 4 (2.3) | 2 (0.4) |

Data are n (%).

*Hypersensitivity reactions, renal adverse events (AEs) and increased liver enzymes.

†Hypoglycaemia was defined as blood glucose concentration ≤3.9 mmol/l.

important attribute for an antidiabetes medication because sudden episodes of hypoglycaemia can represent a safety issue for patients [12]. The low risk for hypoglycaemia induction of linagliptin in this study may be explained by the glucose-dependent nature of the incretin effect on which this drug is based [8,11,15,16].

Similarly, another important consideration when selecting a treatment for diabetes is its effect on body weight. Medication-induced weight gain is undesirable in diabetes given that the majority of patients are already obese or overweight, and obesity is a risk factor for diabetes and cardiovascular disease [25,34]. Linagliptin, like other DPP-4 inhibitors, has a neutral effect on body weight [8–10,25,34,35].

The International Diabetes Federation recommends metformin as the initial glucose-lowering therapy for type 2 diabetes [36]. If patients are not adequately controlled on metformin monotherapy, an additional OAD is recommended as add-on therapy, usually a sulphonylurea. However, there is a risk of hypoglycaemia and weight gain with sulphonylureas and they are not tolerated or contraindicated in some patients. For this reason, there have been a number of studies combining DPP-4 inhibitors with metformin [37–41]. The combination resulted in superior glycaemic control exemplified by a greater reduction in HbA1c from baseline and a higher percentage of patients achieving HbA1c concentrations below 7% compared with metformin monotherapy. To summarize, linagliptin 5 mg once daily is an effective, well-tolerated and rational choice for patients with type 2 diabetes inadequately treated with metformin alone.

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## Conflict of Interest

M.-R. T. and J. R. have received honoraria for attending meetings, consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim. I. T., R. K., S. P., K. A. D. and H.-J. W. are employees of Boehringer Ingelheim and have declared that they have no other conflict of interest. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). M.-R. T., J. R., I. T., R. K., K. A. D. and H.-J. W. contributed to the design of the study, participated in data collection, participated in data analysis, and contributed to the writing or revision of the manuscript. S. P. participated in data analysis and contributed to the writing or revision of the manuscript. All authors saw and approved the final version of the manuscript.

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## Appendix

The following principal investigators were involved in the study: *Czech Republic*: M. Brada, T. Brychta, M. Horňáčková, B. Kocourková, L. Kyseláková, L. Okénka and J. Olšovský; *Finland*: J. Alanko, J. Eriksson, L. Niskanen, R. Paul, J. Saltevo and J. Strand; *Greece*: E. Anastaiou, A. Melidonis and G. Piaditis; *India*: P. K. Agarwal, M. Badgandi, S. R. Bisale, R. Boddula, S. A. Chandratreya, A. Gupta, S. S. Gupta, S. Mahadevan, N. Rais, P. V. Rao, S. Reddy, V. Seshiah, M. Thomas and S. Vidyasagar; *Israel*: F. Adawi, T. Herskovits, E. Karnieli, D. Lender, R.

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