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Research: Treatment

Linagliptin improved glycaemic control without weight gain or hypoglycaemia in patients with Type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: a 24-week randomized, double-blind study

M. Bajaj[1], R. Gilman[2], S. Patel[3], J. Kempthorne-Rawson[4], D. Lewis-D'Agostino[4] and H.-J. Woerle[5]

[1]Baylor College of Medicine, Houston, TX, [2]Safe Harbor Clinical Research, East Providence, RI, USA, [3]Boehringer Ingelheim Ltd., Bracknell, UK, [4]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA and [5]Boehringer Ingelheim GmbH and Co. KG, Ingelheim, Germany

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Abstract

Aims To investigate the efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin in patients with Type 2 diabetes mellitus inadequately controlled by a combination of metformin and pioglitazone.

Methods This was a multi-centre, phase 3, randomized, double-blind, placebo-controlled study comparing linagliptin 5 mg once daily (n = 183) and placebo (n = 89) as add-on to metformin and pioglitazone. The primary endpoint was the change from baseline in glycated haemoglobin (HbA_{1c}) after 24 weeks.

Results The placebo-corrected adjusted mean (SE) change in HbA_{1c} from baseline to 24 weeks was –6 (1) mmol/mol [–0.57 (0.13)%] (P < 0.0001). In patients with baseline $HbA_{1c} \geq$ 53 mmol/mol (7.0%), 32.4% of patients in the linagliptin group and 13.8% in the placebo group achieved HbA_{1c} < 53 mmol/mol (7.0%) (odds ratio 2.94; P = 0.0033). The placebo-corrected adjusted mean (SE) change from baseline in fasting plasma glucose at week 24 was –0.57 (0.26) mmol/l [–10.4 (4.7) mg/dl] (P = 0.0280). The incidence of serious adverse events was 2.2% with linagliptin and 3.4% with placebo. Investigator-defined hypoglycaemia occurred in 5.5% of the linagliptin group and 5.6% of the placebo group. No meaningful changes in mean body weight were noted for either group.

Conclusions Linagliptin as add-on therapy to metformin and pioglitazone produced significant and clinically meaningful improvements in glycaemic control, without an additional risk of hypoglycaemia or weight gain (Clinical Trials Registry No: NCT 00996658).

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Introduction

Despite an expanding range of therapeutic treatment options, patients with Type 2 diabetes mellitus often fail to achieve and maintain glycaemic targets. Many patients who initially achieve treatment goals with metformin eventually experience deterioration of glycaemic control because of the progressive decline of β-cell function over time [1]. Consequently, the addition of one or more oral anti-hyperglycaemic drugs is often necessary.

The combination of metformin and pioglitazone is often prescribed to patients with Type 2 diabetes [2]. These two separate classes of drugs have distinct, but complementary, molecular and organ-specific mechanisms of action on insulin resistance, which, when used in combination, may provide a broader coverage of the defects underlying the pathogenesis of Type 2 diabetes [2]. The efficacy of pioglitazone and metformin combination therapy has been proven in clinical trials [3–5].

When HbA_{1c} goals are not achieved with this dual therapy combination, current treatment guidelines recommend that a

Correspondence to: Mandeep Bajaj. E-mail: mandeepbajaj@hotmail.com

What's new?

- Combination therapy of two or more oral anti-hyperglycaemic drugs is often necessary to reach glycaemic targets in patients with Type 2 diabetes mellitus.
- The combination of metformin and pioglitazone is often prescribed, but, when HbA_{1c} goals are not achieved, treatment guidelines recommend adding a third oral anti-hyperglycaemic drug.
- Few studies have evaluated the effects of triple oral therapy with a dipeptidyl peptidase-4 inhibitor, metformin and pioglitazone.
- The results of this study show that linagliptin may be an effective and safe treatment option for patients with Type 2 diabetes who have failed to reach glycaemic targets with metformin and pioglitazone.

third oral anti-hyperglycaemic drug may be added, avoiding the need for insulin therapy [6]. The addition of a dipeptidyl peptidase-4 (DPP-4) inhibitor to this combination is an attractive treatment option, offering an additional complementary mechanism of action. DPP-4 inhibitors increase active levels of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide, increasing insulin secretion and inhibiting glucagon secretion [7]. The increase in GLP-1 may also improve β-cell function [8]. Linagliptin is a once-daily oral DPP-4 inhibitor that is primarily excreted via the enterohepatic system and therefore does not require dose adjustment in patients with renal or hepatic impairment [9,10]. Phase 3 studies have shown that linagliptin improves glycaemic control and has a good tolerability profile, including a low risk for hypoglycaemia and weight gain [11–15].

Few studies have evaluated the effects of triple oral therapy with a DPP-4 inhibitor, metformin and pioglitazone. Both alogliptin [16,17] and sitagliptin [18] improved glycaemic control and were generally well tolerated in combination with metformin and pioglitazone.

The aim of this study was to investigate the efficacy and safety of linagliptin 5 mg once daily compared with placebo as add-on therapy for 24 weeks in patients with Type 2 diabetes and inadequate glycaemic control with metformin and pioglitazone.

Patients and methods

Study design

This phase 3, randomized, placebo-controlled, double-blind study was performed at 52 trial centres in Asia, Europe and North America. The investigators enrolled male and female patients with Type 2 diabetes, who were aged ≥ 18 and < 80 years, with a BMI ≤ 45 kg/m^2 and HbA_{1c} ≥ 58 mmol/mol (7.5%) and ≤ 86 mmol/mol (10.0%) despite receiving a dose of ≥ 1500 mg/day of metformin (or the maximum tolerated dose, if lower) and a dose of 45 mg/day of pioglitazone (or the maximum clinically acceptable dose in the investigators' opinion). Both doses of metformin and pioglitazone were to be unchanged for 12 weeks before informed consent.

Patients were excluded from the trial if they had uncontrolled hyperglycaemia with a glucose level > 13.3 mmol/l (240 mg/dl) after an overnight fast or > 22.2 mmol/l (400 mg/dl) in a randomly performed measurement during placebo run-in and confirmed by a second measurement on a different day; myocardial infarction, stroke or transient ischaemic attack within 3 months before informed consent; impaired hepatic function; or previous gastric bypass surgery. Further exclusion criteria included known hypersensitivity or allergy to the investigational products; misuse of metformin or pioglitazone; alcohol or drug abuse within 3 months before informed consent that would interfere with trial participation; treatment with systemic steroids at the time of informed consent or change in dosage of thyroid hormones within 6 weeks before informed consent; and participation in another trial with an investigational drug within 2 months before informed consent. Patients treated with rosiglitazone, DPP-4 inhibitors, GLP-1 analogues, insulin or anti-obesity drugs within 3 months of enrolment were also excluded. Pre-menopausal women who were nursing, pregnant or not practising an acceptable method of birth control were ineligible.

The trial protocol was approved by the Independent Ethics Committees or Institutional Review Boards of all participating centres, and is accessible at www.clinicaltrials.gov. The study was carried out according to the principles of the Declaration of Helsinki and the International Conference on Harmonization guideline for Good Clinical Practice. All patients gave written informed consent before participation.

Eligible patients underwent a 2-week, open-label, double-blind, placebo run-in period. They were then randomized (2:1) to receive either linagliptin 5 mg once daily orally or placebo for 24 weeks in addition to metformin and pioglitazone. Treatment assignment was by a computer-generated random sequence using an interactive voice response system. Randomization was stratified by centre and baseline HbA_{1c} [< 69 mmol/mol (8.5%) or ≥ 69 mmol/mol (8.5%)].

Rescue medication was permitted during the randomized period if a patient met the following criteria: a confirmed fasting plasma glucose level of > 11.1 mmol/l or a glucose level > 22.2 mmol/l in a randomly performed measurement during the first 12 weeks; or a confirmed fasting plasma glucose level of > 11.1 mmol/l or a glucose level > 22.2 mmol/l in a randomly performed measurement during weeks 13–24. These results were confirmed by two measurements on separate days. Patients were discontinued from the trial if their fasting plasma glucose level remained above these levels despite receiving rescue medication.

Endpoints and assessments

The primary efficacy endpoint was the change from baseline in HbA_{1c} after 24 weeks. Secondary endpoints were the change from baseline in HbA_{1c} and fasting plasma glucose over time, the change from baseline in fasting plasma glucose after 24 weeks, the percentage of patients who attained HbA_{1c} levels < 53 mmol/mol (7.0%) and < 48 mmol/mol (6.5%) after 24 weeks, and the percentage of patients who achieved a reduction of ≥ 6 mmol/mol (0.5%) in HbA_{1c} after 24 weeks. Other endpoints included the use of rescue therapy and changes in homeostasis model assessment [β-cell function (HOMA-%B) and insulin resistance (HOMA-IR)], disposition index, body weight and plasma lipids after 24 weeks.

Safety endpoints included the frequency and intensity of adverse events, including hypoglycaemia, and clinically relevant new or worsening findings in physical examination, vital signs, 12-lead electrocardiogram and clinical laboratory variables. An independent external clinical event committee reviewed treatment-emergent fatal events and suspected events of stroke, myocardial ischaemia (including myocardial infarction), hospitalization for heart failure, stent thrombosis and revascularization procedures.

Statistical analysis

Based on a standard deviation (SD) of change in HbA_{1c} from baseline of 1.2%, 276 patients were required to achieve a power of 90% to detect a 0.5% difference using a 2:1 randomization.

The primary endpoint was evaluated using analysis of covariance (ANCOVA), with 'treatment' as a fixed classification effect, 'baseline HbA_{1c}' as a linear covariate and 'centre' as a random effect. The analysis was conducted on the full analysis set, comprising all randomized participants who were treated with ≥ 1 dose of study medication, had a baseline HbA_{1c} measurement and ≥ 1 on-treatment HbA_{1c} measurement. The last available HbA_{1c} value prior to rescue treatment or prior to the addition of another anti-diabetic agent was used for patients who received rescue therapy, added an anti-diabetic drug or increased the dose of the background treatment during the treatment period (last observation carried forward). In order to assess the impact of utilizing last observation carried forward for missing data, a mixed-model repeated-measurements analysis on the observed results (without imputation for missing data) at each week was performed utilizing the full analysis set. For this analysis, missing data were not imputed and values after the start of rescue medication were set to missing.

Secondary endpoints were assessed in the full analysis set using an ANCOVA model. Fasting plasma glucose was analysed with the additional linear covariate 'fasting plasma glucose at baseline' in an exploratory way. Changes in fasting plasma glucose over time were analysed using descriptive statistics. Although efficacy analyses for HbA_{1c} and fasting plasma glucose were conducted in conventional units, SI conversions are provided.

The impact of treatment on the use of rescue medication was assessed using logistic regression and the time to first use of rescue therapy was evaluated by Kaplan–Meier analysis. For categorical efficacy analyses, non-completers were considered treatment failures. HOMA indices and disposition index were also analysed using an ANCOVA model that included treatment, continuous baseline HbA_{1c}, continuous baseline value of the biomarker or derived index being analysed, and centre as a random effect. Changes in body weight were analysed by descriptive methods.

In general, safety data were analysed using descriptive statistics. Adverse events were coded using the Medical Dictionary for Drug Regulatory Affairs, version 15.0. The time to the onset of the first hypoglycaemic event was analysed by the Kaplan–Meier method.

Results

Patient disposition, demographics and clinical characteristics

Of the 495 participants enrolled, 183 and 89 patients were randomized to receive linagliptin and placebo, respectively (Fig. 1). Of these, 241 patients completed the trial. The proportion of patients who discontinued was greater for France (30.8%) and the USA (25.0%) compared with India (4.3%) and the Philippines (2.2%). The main reason for discontinuation was for 'other' reasons (n = 16): eight patients discontinued in France following marketing suspension of pioglitazone; five patients withdrew consent; one patient withdrew because of a problem with the interactive voice response system; one patient was unable to attend protocol-specified visits; and one patient moved out of state.

Baseline demographics and clinical characteristics were similar between the two groups (Table 1). The mean (SD) age of subjects was 53.8 (9.3) years, mean BMI was 28.2 (5.3) kg/m^2 and mean HbA_{1c} was 69 (9) mmol/mol [8.42 (0.82)%]. The study population consisted mainly of Asian (69%) and white (27%) patients. Median exposure to study drug was 170 and 169 days in the linagliptin and placebo groups, respectively.

Efficacy: changes in HbA_{1c} and fasting plasma glucose

Linagliptin significantly reduced HbA_{1c} levels (Table 2 and Fig. 2). The placebo-corrected adjusted mean (SE) change from baseline at week 24 for linagliptin was –6 (1) mmol/mol; 95% confidence interval –9 to –3 [–0.57 (0.13)%; 95% CI –0.83 to –0.31]; $P < 0.0001$. For the mixed-model repeated-measurements analysis, the placebo-corrected adjusted mean change from baseline in HbA_{1c} was significant ($P < 0.0001$) for each on-treatment visit: week 6, –5 mmol/mol (–0.43%); week 12, –6 mmol/mol (–0.55%); week 18, –6 mmol/mol (–0.54%); and

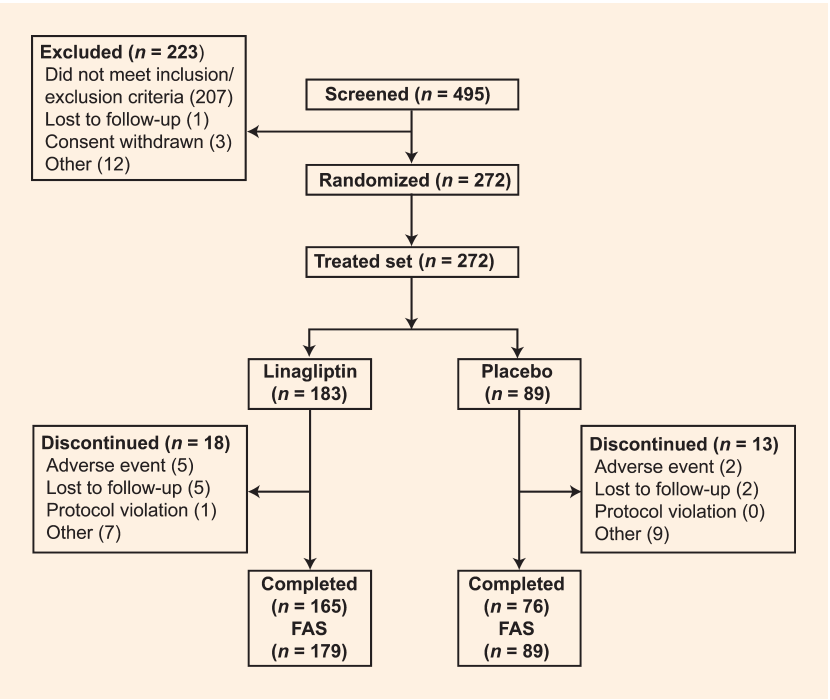

FIGURE 1 Patient allocation. FAS, full analysis set.

week 24; –6 mmol/mol (–0.57%). The difference between treatments did not significantly vary over time ($P = 0.4109$). Linagliptin was superior to placebo in reducing fasting plasma glucose levels (Fig. 3). By week 24, the placebo-corrected adjusted mean (SE) change from baseline in fasting plasma glucose was –0.57 (0.26) mmol/l; 95% CI –1.08 to –0.06 [–10.4 (4.7) mg/dl; 95% CI –19.6 to –1.1]; $P = 0.0280$ (Table 2).

Among patients with baseline HbA_{1c} levels ≥ 53 mmol/mol (7.0%), more than twice as many patients in the linagliptin group than the placebo group achieved HbA_{1c} < 53 mmol/mol (7.0%) and < 48 mmol/mol (6.5%) at week 24 (Fig. 4). More linagliptin patients also achieved a reduction in HbA_{1c} of ≥ 6 mmol/mol (0.5%) after 24 weeks (Fig. 4).

Efficacy: analyses of changes in HbA_{1c} by country

The placebo-corrected adjusted mean (SE) change from baseline in HbA_{1c} after 24 weeks was significant for India and the Philippines: –10 (2) mmol/mol [–0.90 (0.18)%]; $P < 0.0001$ and –9 (4) mmol/mol [–0.80 (0.32)%]; $P = 0.0140$, respectively. The results for the USA (46 patients) indicated a non-significant reduction in HbA_{1c} relative to placebo: –2 (3) mmol/mol [–0.21 (0.31)%]; $P = 0.5136$. The results for France (38 patients) indicated a greater change from baseline in HbA_{1c} after 24 weeks for patients in the placebo group compared with patients in the linagliptin group. The adjusted mean change in HbA_{1c} from baseline was –5 (2) mmol/mol [–0.44 (0.20)%] for linagliptin and –12 (3) mmol/mol [–1.13 (0.31)%] for placebo; placebo-corrected adjusted mean (SE) change from baseline was 8 (4) mmol/mol [0.69 (0.37)%]; $P = 0.0619$.

Efficacy: additional endpoints

On average there was a 27% greater increase from baseline to week 24 in the adjusted geometric mean HOMA-%B with linagliptin compared with placebo that was statistically significant ($P = 0.0055$) (Table 3). The adjusted geometric mean and mean changes from baseline in HOMA-IR and disposition index, respectively, were not significantly different between treatment groups at week 24.

Safety and tolerability

Although the overall frequency of adverse events was greater with linagliptin compared with placebo, drug-related adverse events and serious adverse events were comparable between treatment groups (Table 4). The most frequently reported adverse events in both groups were anaemia (linagliptin: 7.7%; placebo: 6.7%), hyperglycaemia (linagliptin: 6.0%; placebo: 7.9%) and hypoglycaemia (linagliptin: 5.5%; placebo: 4.5%). Adverse events leading to discontinuation of trial medication were low. With the exception of acute myocardial infarction occurring in the placebo group, none of the adverse events leading to premature discontinuation were considered by the investigator to be related to trial medication. The patient who experienced an acute myocardial infarction died and this was the only event adjudicated via the clinical event committee as a cardiovascular event.

Table 1 Baseline demographics and clinical characteristics

	Linagliptin	Placebo
Demographics		
Patients (treated set*), *n*	183	89
Men, *n* (%)	83 (45.4)	49 (55.1)
Race, *n* (%)		
American Indian/Alaska Native	0 (0.0)	1 (1.1)
Asian	125 (68.3)	62 (69.7)
Black or African American	9 (4.9)	2 (2.2)
White	49 (26.8)	24 (27.0)
Age, years, mean (SD)	53.1 (9.7)	55.2 (8.4)
Age groups, *n* (%)		
< 65 years	162 (88.5)	79 (88.8)
65–74 years	20 (10.9)	8 (9.0)
≥ 75 years	1 (0.5)	2 (2.2)
BMI, kg/m^2, mean (SD)	28.2 (5.2)	28.1 (5.5)
Renal function (eGFR) according to the MDRD equation, *n* (%)		
Normal (≥ 90 ml/min)	94 (51.4)	36 (40.4)
Mild impairment (60 to < 90 ml/min)	69 (37.7)	42 (47.2)
Moderate impairment (30 to < 60 ml/min)	14 (7.7)	7 (7.9)
Severe impairment (< 30 ml/min) or end-stage renal disease	0 (0.0)	0 (0.0)
Missing†	6 (6.6)	4 (4.5)
Clinical characteristics		
Patients (full analysis set‡), *n*	179	89
HbA_{1c}, mean (SD)		
mmol/mol	68 (9)	69 (8)
%	8.39 (0.84)	8.47 (0.78)
Fasting plasma glucose, mean (SD)		
mmol/l	8.3 (2.6)	8.4 (2.5)
mg/dl	149.6 (46.5)	151.3 (45.4)
Time since diagnosis of diabetes, *n* (%)		
> 5 years	22 (12.3)	6 (6.7)
> 1 to ≤ 5 years	73 (40.8)	45 (50.6)
≤ 1 year	84 (46.9)	38 (42.7)

*All patients who were treated with ≥ 1 dose of study medication.
†For these patients, no valid baseline estimated glomerular filtration rate (eGFR) or creatinine measurement was available; therefore the value was set to missing.
‡All patients who had a baseline and ≥ 1 on-treatment HbA_{1c} measurement.
MDRD, Modification of Diet in Renal Disease.

No patients were adjudicated with hospitalization for heart failure. There were no reports of pancreatitis or heart failure.

The percentage of patients with investigator-defined hypoglycaemia at week 24 was similar between groups (Table 5). No severe episodes of hypoglycaemia (requiring external assistance) occurred. There were no clinically relevant changes in vital signs or laboratory variables in either group, including no between-group imbalance in shifts in stage of renal impairment.

The median changes from baseline to last value on treatment were small and similar for total cholesterol and HDL cholesterol. Differences between the treatment groups in median change from baseline were noted for triglycerides (linagliptin: –3 mg/dl; placebo: 7 mg/dl) and LDL cholesterol (linagliptin: 3 mg/dl; placebo: –28 mg/dl).

Rescue medication was required by 7.3% of patients in the linagliptin group and 4.5% of patients in the placebo group. The odds of requiring rescue medication were not different between groups (odds ratio: 1.760; $P < 0.3463$). The adjusted mean (SE) body weight did not change significantly from baseline to week 24 [linagliptin: 0.50 (0.29) kg; placebo: 0.67 (0.35) kg].

Discussion

This phase 3 trial evaluated the efficacy and safety of linagliptin 5 mg once daily in patients with Type 2 diabetes inadequately controlled on metformin and pioglitazone. The addition of linagliptin provided clinically meaningful improvements in glycaemic control, without increasing the risk for hypoglycaemia or weight gain.

Previous studies have shown that DPP-4 inhibitors can improve glycaemic control when administered with metformin and pioglitazone, without increasing the risk for hypoglycaemia. The placebo-corrected adjusted reduction in HbA_{1c} observed in this study is comparable with the reductions observed with alogliptin [16,17] and sitagliptin [18]. However, because of differences in study design and variations in patient populations, it is difficult to compare the results from these clinical trials.

Table 2 Adjusted means for the change from baseline at week 24 in HbA_{1c} and fasting plasma glucose (full analysis set, last observation carried forward)

	Linagliptin	Placebo
HbA_{1c}		
Patients*, *n*	179	89
Mean at baseline, mmol/mol (SE)	68 (1)	69 (1)
Change from baseline, mmol/mol (SE)	–10 (1)	–4 (1)
Adjusted† mean change from baseline, mmol/mol (SE)	–9 (1)	–3 (2)
Difference vs. placebo		
Adjusted† mean, mmol/mol (SE)	–6 (1)	
95% CI	–9 to –3	
P-value	< 0.0001	
Mean at baseline, % (SE)	8.39 (0.06)	8.47 (0.08)
Change from baseline, % (SE)	–0.92 (0.08)	–0.40 (0.12)
Adjusted† mean change from baseline, % (SE)	–0.84 (0.11)	–0.27 (0.13)
Difference vs. placebo		
Adjusted† mean, % (SE)	–0.57 (0.13)	
95% CI	–0.83 to –0.31	
P-value	< 0.0001	
Fasting plasma glucose		
Patients*, *n*	175	86
Mean at baseline, mmol/l (SE)	8.26 (0.19)	8.39 (0.27)
Change from baseline, mmol/l (SE)	–0.55 (0.18)	–0.04 (0.26)
Adjusted‡ mean change from baseline, mmol/l (SE)	–0.57 (0.15)	0.00 (0.21)
Difference vs. placebo		
Adjusted‡ mean, mmol/l (SE)	–0.57 (0.26)	
95% CI	–1.08 to –0.06	
P-value	0.0280	
Mean at baseline, mg/dl (SE)	148.9 (3.5)	151.3 (4.9)
Change from baseline, mg/dl (SE)	–9.9 (3.2)	–0.7 (4.8)
Adjusted‡ mean change from baseline, mg/dl (SE)	–10.3 (2.7)	0.1 (3.8)
Difference vs. placebo		
Adjusted‡ mean, mg/dl (SE)	–10.4 (4.7)	
95% CI	–19.6 to –1.1	
P-value	0.0280	

*All patients who had a baseline and ≥ 1 on-treatment HbA_{1c} measurement.
†Adjusted model includes treatment, baseline HbA_{1c} and centre as random.
‡Adjusted model includes treatment, baseline HbA_{1c}, baseline fasting plasma glucose and centre as random.

The change from baseline in HbA_{1c} was affected by country, as seen in India and the Philippines—the two countries representing Asia in the trial. Evidence suggests that DPP-4 inhibitors may elicit glucose-lowering effects in Asians that exceed those observed in other ethnic groups, although the underlying mechanisms are not well understood [19]. Conversely, the result for France indicated a greater change in HbA_{1c} with placebo compared with linagliptin. This unexpected finding may be attributed to the low number of patients enrolled there.

The addition of linagliptin to metformin and pioglitazone was generally well tolerated, showing a similar safety profile to that observed in previous clinical trials with linagliptin [11,14,15,20] and those evaluating triple oral therapy with a DPP-4 inhibitor, metformin and pioglitazone [16–18]. Although the incidence of adverse events was higher with linagliptin compared with placebo, this was because of a wide range of adverse events. Despite the intensified treatment strategy, the incidence of hypoglycaemia was low and comparable with placebo. It is believed that DPP-4 inhibitors enhance α-cell responsiveness to low ambient glucose concentrations [21,22], which may explain the low risk for hypoglycaemia with linagliptin.

Because of the progressive decline of β-cell function in Type 2 diabetes, most patients eventually require intensification of anti-diabetes therapy to maintain glycaemic control [1]. Given the complementary mechanisms of action of linagliptin, metformin and pioglitazone, triple combination therapy with these oral anti-hyperglycaemic drugs is theoretically an attractive treatment strategy [7,23–25]. These results support the use of this combination as an effective third-line therapeutic option when dual therapy with metformin and pioglitazone fails. HOMA-%B significantly increased at week 24 compared with placebo, suggesting that this combination may improve β-cell function. This finding is consistent with linagliptin's mechanism of action and has been observed in previous clinical trials [11,12,14,15]. Although increasing the number of prescribed drugs can increase the potential for side effects and drug–drug interactions [26], no safety concerns emerged. Treatment-induced hypoglycaemia is a major concern in patients with Type 2 diabetes and some oral anti-hyperglycaemic drugs, such as sulphonylureas, are associated with an

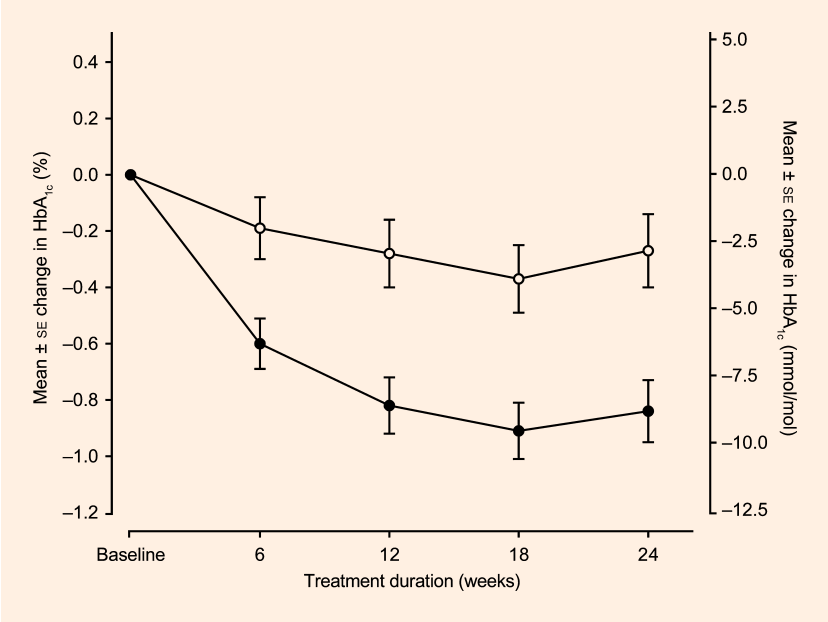

FIGURE 2 Adjusted mean change from baseline in HbA_{1c} over time (full analysis set, last observation carried forward). Linagliptin 5 mg once daily (•); placebo (○).

increased risk of hypoglycaemia [12,24]. In a clinical trial evaluating the efficacy of glimepiride as add-on to metformin and a thiazolidinedione, significantly more episodes of hypoglycaemia and weight gain were reported with triple therapy compared with placebo [27]. DPP-4 inhibitors are generally associated with a low risk of hypoglycaemia and are weight neutral. In this study, hypoglycaemia was uncommon and there was no change in body weight. This triple combination therapy therefore may be a valuable treatment option for patients with Type 2 diabetes who are failing to achieve glycaemic targets.

An important limitation of this study was that the addition of linagliptin was compared only with placebo. In clinical practice, patients and their physicians would consider other

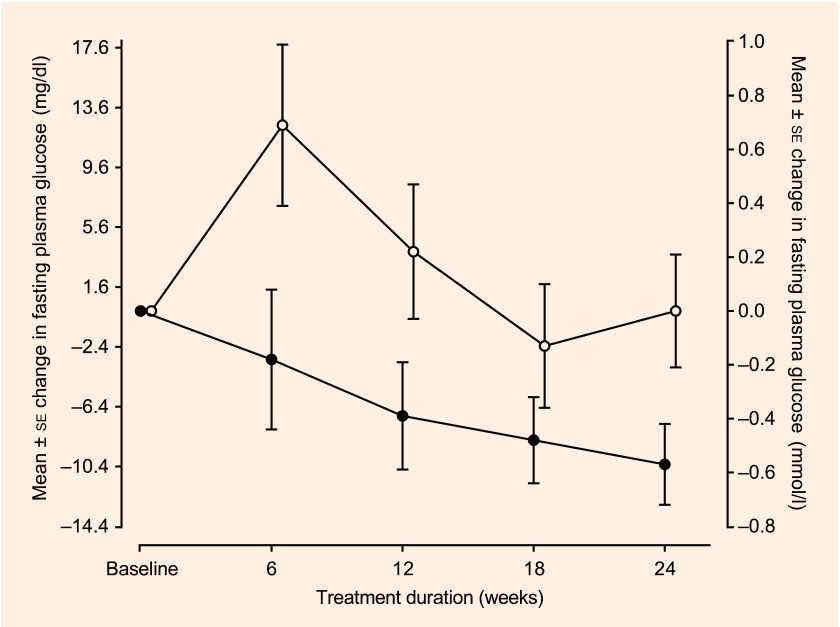

FIGURE 3 Adjusted mean change from baseline in fasting plasma glucose over time (full analysis set, last observation carried forward). Linagliptin 5 mg once daily (•); placebo (○).

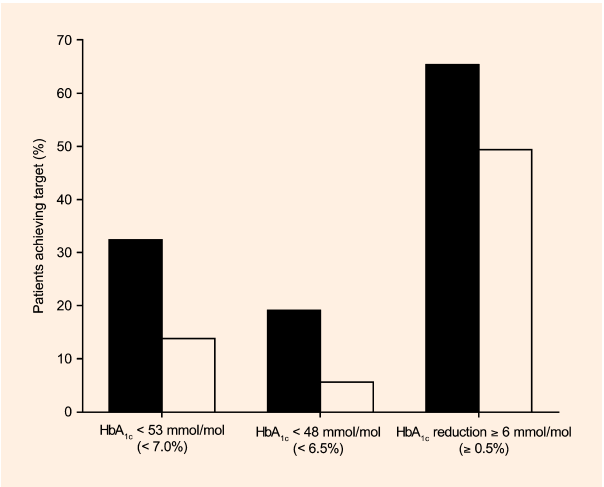

FIGURE 4 Percentage of patients achieving HbA_{1c} < 53 mmol/mol, < 48 mmol/mol or ≥ 6 mmol/mol reduction after 24 weeks (full analysis set, non-completers were considered treatment failures). Linagliptin 5 mg once daily (■); placebo (□).

treatment options, such as increasing the doses of either oral anti-hyperglycaemic drug, adding an additional oral anti-hyperglycaemic drug or initiating insulin therapy [6]. Another limitation is that this study was conducted primarily in Asians and therefore further studies may be required to confirm the efficacy and tolerability of linagliptin with this combination in patients of non-Asian ethnicities.

Linagliptin as add-on therapy to metformin and pioglitazone improved glycaemic control without increasing the risk for hypoglycaemia or weight gain. The addition of linagliptin may be a valuable third-line treatment option in patients with Type 2 diabetes who have failed to achieve glycaemic targets with metformin and pioglitazone dual therapy, and may be used in preference to initiating insulin therapy.

Funding sources

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Table 3 Adjusted mean change from baseline in fasting biomarkers and derived indices at week 24 (full analysis set, last observation carried forward)

	Linagliptin	Placebo
HOMA-%B [(mU/l)/(mmol/l)]		
Patients with baseline and on-treatment results, *n*	138	69
Baseline, gMean (gCV)	43.75 (110.63)	44.58 (87.67)
Relative change from baseline		
Adjusted* gMean ratio, %	1.41	1.11
95% CI	1.14–1.74	0.88–1.39
Comparison vs. placebo		
Adjusted* gMean ratio, %	1.27	
95% CI	1.07–1.50	
P-value	0.0055	
HOMA-IR [(mU/l) × (mmol/l)]		
Patients with baseline and on-treatment results, *n*	139	69
Baseline, gMean (gCV)	2.91 (83.50)	2.97 (75.01)
Relative change from baseline		
Adjusted† gMean ratio, %	1.05	1.10
95% CI	0.95–1.16	0.95–1.27
Comparison vs. placebo		
Adjusted† gMean ratio, %	0.96	
95% CI	0.80–1.14	
P-value	0.6023	
Disposition index [1/((mmol/l) × (mmol/l))]		
Patients, *n*	148	71
Baseline, mean (SE)	24.67 (4.53)	22.56 (3.75)
Change from baseline		
Adjusted‡ mean (SE)	14.53 (18.39)	10.13 (18.50)
Comparison vs. placebo		
Adjusted‡ mean (SE)	4.41 (3.62)	
95% CI	–2.74 to 11.55	
P-value	0.2255	

*Adjusted model includes treatment, continuous baseline HbA_{1c}, continuous HOMA-%B at baseline and centre as random.
†Adjusted model includes treatment, continuous baseline HbA_{1c}, continuous HOMA-IR at baseline and centre as random.
‡Adjusted model includes treatment, continuous baseline HbA_{1c}, continuous disposition index at baseline and centre as random.
gMean, geometric mean
HOMA-%B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 4 Overall summary of adverse events (treated set)

	Linagliptin	Placebo
Patients*, *n*	183	89
Any adverse event, *n* (%)	114 (62.3)	43 (48.3)
Severe adverse events, *n* (%)	4 (2.2)	1 (1.1)
Drug-related adverse events, *n* (%)	21 (11.5)	12 (13.5)
Adverse events leading to discontinuation of trial medication, *n* (%)	5 (2.7)	2 (2.2)
Serious adverse events, *n* (%)	4 (2.2)	3 (3.4)
Fatal, *n* (%)	0 (0.0)	1 (1.1)
Increase in amylase, *n* (%)	2 (1.1)	1 (1.1)
Pancreatitis, *n* (%)	0 (0.0)	0 (0.0)
Pancreatic cancer, *n* (%)	0 (0.0)	0 (0.0)
Colon cancer, *n* (%)	1 (0.5)	0 (0.0)
Patients with cardiovascular death, myocardial infarction, stroke or unstable angina, *n* (%)	0 (0.0)	1 (1.1)

*All patients who were treated with ≥ 1 dose of study medication.

Table 5 Investigator-defined hypoglycaemia (treated set)

	Linagliptin	Placebo
Patients*, *n*	183	89
Hypoglycaemic adverse events, *n* (%)	10 (5.5)	5 (5.6)
Any documented symptomatic hypoglycaemia† and measured plasma glucose ≤ 70 mg/dl	2 (1.1)	3 (3.4)
Any documented symptomatic hypoglycaemia‡ and measured plasma glucose < 54 mg/dl	1 (0.5)	2 (2.2)
Any severe hypoglycaemic episode§	0 (0.0)	0 (0.0)

*All patients who were treated with ≥ 1 dose of study medication.
†Accompanied by typical symptoms of hypoglycaemia.
‡Accompanied by typical symptoms of hypoglycaemia but no need for external assistance.
§Requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

Competing interests

MB has received research grant support from Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Eli Lilly and Amylin. MB has also received honoraria for advisory panel participation for Takeda Pharmaceuticals and Sanofi Aventis and has received lecture fees from Takeda Pharmaceuticals, Boehringer Ingelheim and Eli Lilly. SP, JK-R, DL-D and H-JW are employees of Boehringer Ingelheim. RG has nothing to declare.

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Previous presentation

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