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ORIGINAL ARTICLE

Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study

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Aims: To compare the efficacy, safety and tolerability of linagliptin or placebo administered for 24 weeks in combination with pioglitazone in patients with type 2 diabetes mellitus (T2DM) exhibiting insufficient glycaemic control (HbA1c 7.5–11.0%).

Methods: Patients were randomized to receive the initial combination of 30 mg pioglitazone plus 5 mg linagliptin (n = 259) or pioglitazone plus placebo (n = 130), all once daily. The primary endpoint was change from baseline in HbA1c after 24 weeks of treatment, adjusted for baseline HbA1c and prior antidiabetes medication.

Results: After 24 weeks of treatment, the adjusted mean change (±s.e.) in HbA1c with the initial combination of linagliptin plus pioglitazone was −1.06% (±0.06), compared with −0.56% (±0.09) for placebo plus pioglitazone. The difference in adjusted mean HbA1c in the linagliptin group compared with placebo was −0.51% (95% confidence interval [CI] −0.71, −0.30; $p < 0.0001$). Reductions in fasting plasma glucose (FPG) were significantly greater for linagliptin plus pioglitazone than with placebo plus pioglitazone; −1.8 and −1.0 mmol/l, respectively, equating to a treatment difference of −0.8 mmol/l (95% CI −1.2, −0.4; $p < 0.0001$). Patients taking linagliptin plus pioglitazone, compared with those receiving placebo plus pioglitazone, were more likely to achieve HbA1c of <7.0% (42.9 vs. 30.5%, respectively; $p = 0.0051$) and reduction in HbA1c of ≥0.5% (75.0 vs. 50.8%, respectively; $p < 0.0001$). β-cell function, exemplified by the ratio of relative change in adjusted mean HOMA-IR and disposition index, improved. The proportion of patients that experienced at least one adverse event was similar for both groups. Hypoglycaemic episodes (all mild) occurred in 1.2% of the linagliptin plus pioglitazone patients and none in the placebo plus pioglitazone group.

Conclusion: Initial combination therapy with linagliptin plus pioglitazone was well tolerated and produced significant and clinically meaningful improvements in glycaemic control. This combination may offer a valuable additive initial treatment option for T2DM, particularly where metformin either is not well tolerated or is contraindicated, such as in patients with renal impairment.

Keywords: DPP-4 inhibitor, GIP, GLP-1, glycaemic control, HbA1c, incretin therapy, linagliptin, type 2 diabetes

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Introduction

A progressive decline in pancreatic β-cell function and chronic insulin resistance characterizes type 2 diabetes mellitus (T2DM) [1], which accounts for 90% of the 220 million cases of diabetes worldwide [2]. Decreased β-cell mass and function probably contribute to the declining efficacy of chronic antidiabetes treatment. Within the 3 years following diagnosis, 50% of T2DM patients require combination therapy to attain HbA1c targets. By 9 years, three-quarters require combination therapy [3]. Combination therapy employs agents with complementary mechanisms of action to produce an additive or synergistic improvement in glycaemic control while minimizing the incidence of unwanted side effects [4]. Concomitant treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor and a thiazolidinedione is therefore mechanistically rational, and specific combinations can avoid the risk of exacerbating certain adverse events.

Linagliptin (5 mg once daily) is a novel DPP-4 inhibitor, with a unique xanthine-based structure [5]. An *in vitro* study showed that linagliptin inhibited DPP-4 with an IC_{50} of ~1 nM, compared with sitagliptin (19 nM), alogliptin (24 nM), saxagliptin (50 nM) and vildagliptin (62 nM) [5]. In animal models, DPP-4 inhibition 24 h after linagliptin administration was greater than that produced by saxagliptin, alogliptin,

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vildagliptin and sitagliptin, with ED_{50} values for inhibition of plasma DPP-4 activity calculated as 0.9, 2.7, 10, 14 and >30 mg/kg, respectively [5]. In healthy volunteers, single doses of 2.5 and 5.0 mg linagliptin reduced DPP-4 activity by 72.7 and 86.1%, respectively [6]. The long terminal half-life of linagliptin together with the sustained inhibition of DPP-4 (>80% at 24 h at steady state) support once-daily dosing [6–8].

The pharmacokinetics of linagliptin differs from that of other DPP-4 inhibitors. For example, less than 7% of a dose of linagliptin undergoes renal excretion [9] whereas approximately 80 and 85% of an oral dose of sitagliptin and vildagliptin, respectively, is excreted unchanged in the urine [10,11]. In contrast, linagliptin is excreted via the enterohepatic system with ~85% excreted unchanged in the faeces [9]. The pharmacokinetic profile of linagliptin may avoid the need to adjust the dose in patients with renal impairment, hepatic insufficiency, as well as in elderly or obese patients.

Moreover, linagliptin is not a clinically relevant substrate or inhibitor of cytochrome P450 isoenzymes [9] or P-glycoprotein. Therefore, linagliptin co-administration is not associated with clinically relevant effects on the pharmacokinetics or pharmacodynamics of other drugs commonly prescribed to patients with T2DM, such as metformin [12], pioglitazone [13], glyburide [14], simvastatin [15], warfarin [16], digoxin [17] or oral contraceptives [18].

The objective of this Phase III trial was to compare the efficacy, safety and tolerability of linagliptin (5 mg) and placebo when administered once daily for 24 weeks in combination with pioglitazone (30 mg once daily) in patients with T2DM and insufficient glycaemic control (HbA1c 7.5–11.0%).

Materials and Methods

Study Population and Design

This randomized, placebo-controlled, double-blind, parallel-group study enrolled drug-naïve or previously treated T2DM patients with insufficient glycaemic control and was carried out between 15 April 2008 and 19 June 2009 (Linagliptin Protocol 1218.15; ClinicalTrials.gov NCT00641043). Patients were enrolled at 43 sites across seven countries (Austria, Greece, Hungary, Japan, Portugal, Romania and Spain). Before randomization, T2DM patients pre-treated with oral antidiabetes drugs (OADs) underwent washout for 4 weeks followed by a 2-week placebo run-in. Drug-naïve patients entered the 2-week placebo run-in. Patients then received the initial combination of 30 mg pioglitazone and linagliptin (5 mg) or 30 mg pioglitazone and placebo orally, all once daily, for 24 weeks.

Inclusion and Exclusion Criteria

The study enrolled male and female T2DM patients (aged ≥18 and ≤80 years) who showed inadequate glycaemic control. At baseline, patients had HbA1c concentrations between 7.5 and 11.0%. At screening, patients had body mass indices (BMI) of ≤40 kg/m^2.

Patients were excluded if they had another clinical condition that was deemed by the investigators as possibly compromising the study's safe conduct. Such conditions included: myocardial infarction, stroke, transient ischaemic attack or diabetic ketoacidosis within 6 months of enrolment; impaired hepatic function; known hypersensitivity or allergy to the study drugs or their excipients; treatment with GLP-1 analogues or agonists, insulin or anti-obesity drugs during the 3 months before enrolment. The study also excluded pre-menopausal women who were nursing, pregnant or of childbearing potential and not practising birth control and patients with fasting blood glucose >13.3 mmol/l (240 mg/dl) at screening.

Study Medication and Randomization

Boehringer Ingelheim provided linagliptin and matching placebo tablets, as well as over-encapsulated pioglitazone (Actos®, Eli Lilly & Co., Vienna, Austria). Patients received one tablet and one capsule orally, once daily. Patients who remained eligible at the end of the 2-week placebo run-in were randomly assigned to linagliptin or placebo in a 2 : 1 ratio determined by a computer-generated random sequence, stratified by HbA1c (<8.5 vs. ≥8.5%) and previous use of OAD (none, monotherapy, combination therapy). The placebo run-in period of this trial was performed open-label and the randomized period was performed double-blind.

The use of metformin (or other OAD if metformin was not tolerated or contraindicated) as rescue medication could be initiated during the first 12 weeks of randomized treatment and 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 could 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. 'Confirmed' was defined as a minimum of two measurements performed on different days, with at least one measurement evaluated at the investigational site. The patient was discontinued from the study if fasted glucose levels remained >13.3 mmol/l during the first 12 weeks of randomized treatment or >11.1 mmol/l during the last 12 weeks of randomized treatment despite the initiation of rescue therapy.

Ethics and Good Clinical Practice

All participants provided written informed consent. The protocol was approved by the independent ethics committee/institutional review board at each study site, and the study was conducted in accordance with the Declaration of Helsinki, using Good Clinical Practice.

Criteria for Evaluation

The primary endpoint was change from baseline in HbA1c after 24 weeks of treatment, adjusted for baseline HbA1c and prior antidiabetes medication. Secondary endpoints included: the percentage of patients achieving an HbA1c <7.0%, the proportion that showed a reduction in HbA1c of at least 0.5% after 24 weeks of treatment and reduction from baseline in HbA1c over time. Other secondary endpoints were change from baseline in fasting plasma glucose (FPG) over time and

after 24 weeks of treatment, as well as changes in markers of β-cell function, assessed using the homeostasis model assessment for insulin resistance (HOMA-IR), β-cell function (HOMA-β) and the disposition index (DI). Investigators evaluated safety based on the incidence and intensity of adverse events, physical examination, 12-lead electrocardiogram (ECG), vital signs and clinical laboratory parameters. Hypoglycaemic episodes were defined as follows: asymptomatic hypoglycaemia (episode not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration of $\leq$3.9 mmol/l); documented symptomatic hypoglycaemia with a measured plasma glucose concentration of $\geq$3.0 and $\leq$3.9 mmol/l (episode accompanied by typical symptoms of hypoglycaemia); documented symptomatic hypoglycaemia with a measured plasma glucose concentration of <3.0 mmol/l (episode accompanied by typical symptoms of hypoglycaemia but no need for external assistance); and severe hypoglycaemia (episode requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions). Hypoglycaemic episodes could be reported as adverse events (medical judgement was used to determine the causal relationship between the investigational drug and an adverse event). Compliance was assessed by tablet count.

HbA1c, FPG and vital signs were measured at each visit during the study. Fasting insulin levels were measured at baseline and week 24. Standard haematology and biochemistry laboratory assessments were made at each visit. Fasting lipid levels [triglycerides, total-, low-density lipoprotein (LDL)-, high-density lipoprotein (HDL)-, non-HDL- and very low-density lipoprotein (VLDL)-cholesterol] were measured and ECGs were performed at screening and at weeks 0, 12 and 24.

Routine laboratory investigations (haematology, clinical chemistry and urinalysis) and the determination of HbA1c levels were performed by a central laboratory (MDS Pharma Services Central Laboratories, facilities in France and Singapore). The determination of plasma glucose and insulin to assess HOMA-indices for insulin secretion and insulin resistance was performed by MDS Pharma Services, France. Assays were performed according to standardized and validated procedures according to Good Laboratory Practice.

Statistical Methods

The primary endpoint was tested using a superiority hypothesis versus placebo employing analysis of covariance (ANCOVA). Treatment and previous OAD were fixed classification effects and baseline HbA1c was a linear covariate. The ANCOVA used a two-sided 5% level of significance. Descriptive statistics summarized secondary and safety endpoints. The full analysis set (FAS) consisted of randomized patients treated with at least one dose of study medication and who had a baseline and at least one on-treatment HbA1c measurement, equating to an intention to treat (ITT) analysis. All treated subjects who had received at least one dose of trial medication (treated set) were included in the analysis of safety. Unless otherwise stated, the results in this paper derive from the FAS.

Assuming a standard deviation of 1.6% for the difference in HbA1c from baseline, a total number of 125 patients in the placebo group and 250 in the linagliptin group were required to achieve a power of 97% to detect a 0.7% difference in HbA1c change from baseline.

Results

Patient Disposition and Demographics

Investigators enrolled 707 patients and randomized 389 to receive pioglitazone 30 mg plus either placebo (130 patients) or linagliptin 5 mg (259 patients). Failure to meet inclusion HbA1c levels was the most common reason for enrolled patients not being randomized. Figure 1 summarizes patient disposition. Overall, 14.6 and 5.8% of the placebo and linagliptin arms withdrew prematurely. At baseline, demographic characteristics and HbA1c were comparable between groups (Table 1). In total, four patients in the placebo group and 12 patients in the linagliptin group had received a glitazone in prior treatment. The FAS consisted of 128 patients receiving placebo plus pioglitazone and 252 patients receiving linagliptin plus pioglitazone

Change in HbA1c

The placebo-corrected difference in the adjusted mean change from baseline in HbA1c increased over the first 12 weeks (reaching −0.50%) and remained constant until week 24. After 24 weeks of treatment, the adjusted mean (±s.e.) change in HbA1c from baseline for linagliptin plus pioglitazone was −1.06% (±0.06) compared with −0.56% (±0.09) for placebo plus pioglitazone (Table 2). The difference in the adjusted mean HbA1c between the linagliptin and placebo groups was −0.51% [95% confidence interval (CI) −0.71, −0.30; $p < 0.0001$], with the linagliptin plus pioglitazone arm showing the greater reduction. After 24 weeks of treatment, 42.9% of patients in the linagliptin plus pioglitazone group and 30.5% in the placebo plus pioglitazone group achieved HbA1c <7.0% (odds ratio 2.1, 95% CI 1.3, 3.5; $p = 0.0051$) (Table 3). Moreover, 75.0 and 50.8% of patients, respectively, achieved an HbA1c reduction of $\geq$0.5% at 24 weeks (odds ratio 3.8, 95% CI 2.3, 6.4; $p < 0.0001$).

Linagliptin plus pioglitazone produced a larger reduction in non-adjusted HbA1c over time than placebo plus pioglitazone ($p < 0.0001$ at each visit, figure 2). Figures 3a and 3b show the non-adjusted change in HbA1c over time for patients stratified into subgroups according to whether they had been pre-treated with any OAD and therefore underwent washout or were treatment naïve. The absolute change from baseline was greater for the patients not requiring washout, but the placebo-corrected change was greater for the pre-treated patients (−0.68% and −0.34%, respectively).

The reduction in HbA1c was greatest for patients with higher baseline HbA1c (figure 4). Linagliptin plus pioglitazone patients with a baseline HbA1c $\geq$9.0% had a larger reduction in HbA1c (−1.49%) than seen in the overall patient group receiving linagliptin plus pioglitazone (−0.90%). The placebo-corrected adjusted mean change from baseline at 24 weeks for this subgroup was −0.65% (95% CI −1.02, −0.28; $p = 0.0008$). For the subgroups of patients with baseline HbA1c 7.5 to <8.0% and 8.0 to <9.0%, the placebo-corrected adjusted mean changes from baseline at week 24 were −0.48% (95% CI −0.95, −0.01;

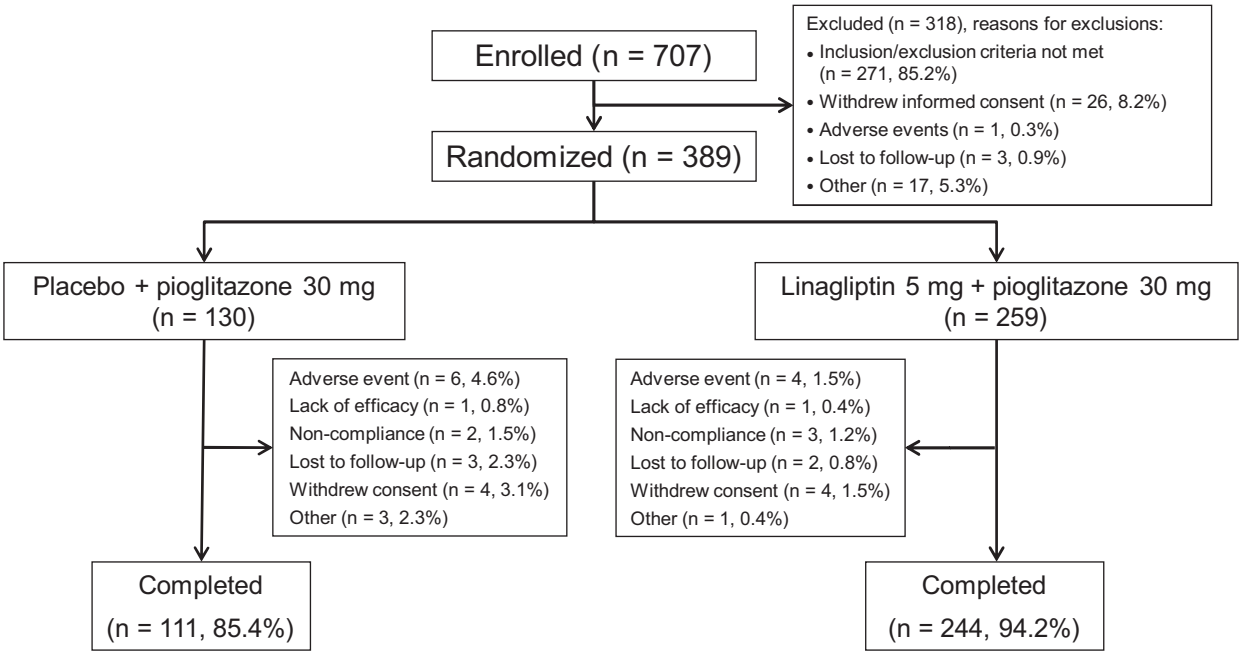

Figure 1. Flow diagram of patient disposition.

p = 0.048) and −0.49% (95% CI −0.82, −0.16; p = 0.0031), respectively.

Fasting Plasma Glucose

After 24 weeks of treatment, the adjusted mean change in FPG in the linagliptin plus pioglitazone group was −1.8 mmol/l (±0.1) compared with −1.0 mmol/l (±0.2) for placebo plus pioglitazone (Table 2), a difference of −0.8 mmol/l (p < 0.0001). Non-adjusted means of FPG declined to a greater extent during the first 6 weeks of treatment with linagliptin plus pioglitazone (10.5–8.5 mmol/l) than with placebo plus pioglitazone (10.6–9.3 mmol/l) (figure 5). From weeks 6 to 24, mean FPG for linagliptin plus pioglitazone remained relatively constant (~8.4 mmol/l). In patients receiving placebo plus pioglitazone, FPG declined between weeks 6 and 12 (9.3–9.1 mmol/l) and then remained constant until week 24. The adjusted mean change from baseline in FPG between groups was −0.73 mmol/l (95% CI −1.08, −0.39; p < 0.0001) and −0.79 mmol/l (95% CI −1.17, −0.41; p < 0.0001) at weeks 12 and 24, respectively, with the linagliptin arm showing the greater reduction over the placebo arm at both time-points.

Rescue Medication

The proportion of patients requiring rescue medication was 7.9% in the linagliptin plus pioglitazone group versus 14.1% with placebo plus pioglitazone (odds ratio 0.45, 95% CI 0.21, 0.95; p = 0.035).

Markers of β-cell Function

At week 24, the adjusted mean change from baseline for HOMA-IR was −2.90 for linagliptin plus pioglitazone and −2.58 for placebo plus pioglitazone (Table 4). The difference between the linagliptin and placebo arms was −0.32 (95% CI −0.77, 0.13; p = 0.16). The ratio of relative change in adjusted geometric mean HOMA-IR showed a difference for linagliptin plus pioglitazone versus placebo plus pioglitazone of 0.85 (95% CI 0.75, 0.96; p = 0.0076).

The adjusted mean change from baseline in HOMA-β (−2.17 for linagliptin plus pioglitazone and −1.44 for placebo plus pioglitazone) was −0.73 at week 24 (95% CI −9.16, 7.70; p = 0.86). Similarly, the adjusted geometric mean for the ratio of relative change at week 24 in the linagliptin plus pioglitazone and placebo plus pioglitazone arms was 1.01 (95% CI 0.89, 1.16; p = 0.85). DI increased in both groups throughout the study. By week 24, the adjusted mean change from baseline for linagliptin plus pioglitazone was 6.56, and 3.87 for placebo plus pioglitazone, equivalent to a difference of 2.69 (95% CI 0.65, 4.74; p = 0.010).

Change in Body Weight

By week 24, mean weight had increased in both groups compared with baseline. The adjusted mean change was greater with linagliptin plus pioglitazone (2.3 kg) than with placebo plus pioglitazone (1.2 kg) with a 1.1 kg difference (95% CI 0.2, 2.0; p = 0.014 for between-group comparison). The mean weight for linagliptin plus pioglitazone patients was lower than that of placebo plus pioglitazone patients both at baseline (78.3 and 82.7 kg, respectively) and at week 24 (80.8 and 84.0 kg, respectively).

Safety and Tolerability

The safety analysis included 389 patients who received at least one dose of trial medication. Overall, the proportion

Table 1. Demographics and baseline characteristics.

	Placebo + pioglitazone 30 mg	Linagliptin 5 mg + pioglitazone 30 mg	Total
Number of patients, n	130	259	389
Gender, n (%)			
Male	85 (65.4)	152 (58.7)	237 (60.9)
Female	45 (34.6)	107 (41.3)	152 (39.1)
Race, n (%)			
American Indian/Alaska Native	1 (0.8)	1 (0.4)	2 (0.5)
Asian	32 (24.6)	65 (25.1)	97 (24.9)
White	97 (74.6)	193 (74.5)	290 (74.6)
Ethnicity, n (%)			
Not Hispanic/Latino	120 (92.3)	246 (95.0)	366 (94.1)
Hispanic/Latino	9 (6.9)	12 (4.6)	21 (5.4)
Missing	1 (0.8)	1 (0.4)	2 (0.5)
Age (years)			
Mean (s.d.)	57.1 (10.1)	57.7 (9.6)	57.5 (9.8)
Age groups (years), n (%)			
<65	95 (73.1)	195 (75.3)	290 (74.6)
65–74	30 (23.1)	58 (22.4)	88 (22.6)
≥75	5 (3.8)	6 (2.3)	11 (2.8)
Baseline weight (kg)			
Mean (s.d.)	82.7 (15.8)	78.3 (15.6)	79.8 (15.8)
Baseline BMI (kg/m^2)			
Mean (s.d.)	29.7 (4.8)	28.7 (4.8)	29.0 (4.9)
Baseline BMI, categorical (kg/m^2), n (%)			
<30	68 (52.3)	157 (60.6)	225 (57.8)
≥30	62 (47.7)	102 (39.4)	164 (42.2)
Baseline eGFR (MDRD staging) ($ml/min/1.73\ m^2$), n (%)			
≥90	64 (49.2)	140 (54.1)	204 (52.4)
60 to <90	55 (42.3)	97 (37.5)	152 (39.1)
30 to <60	5 (3.8)	12 (4.6)	17 (4.4)
Missing	6 (4.6)	10 (3.9)	16 (4.1)
HbA1c (%)			
Number of patients, n	128	252	380
Baseline			
Mean (s.d.)	8.58 (0.87)	8.60 (0.79)	8.59 (0.82)
Baseline HbA1c, categorical, n (%)			
<7.0%	0 (0.0)	0 (0.0)	0 (0.0)
7.0 to <8.0%	35 (27.3)	59 (23.4)	94 (24.7)
8.0 to <9.0%	52 (40.6)	115 (45.6)	167 (43.9)
≥9.0%	41 (32.0)	78 (31.0)	119 (31.3)
Number of prior antidiabetic drugs, n (%)			
0	65 (50.8)	124 (49.2)	189 (49.7)
1	40 (31.3)	81 (32.1)	121 (31.8)
≥2	23 (18.0)	47 (18.7)	70 (18.4)
FPG (mmol/l)			
Number of patients, n	128	251	379
Baseline			
Mean (s.d.)	10.6 (2.4)	10.5 (2.4)	10.6 (2.4)

eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease equation; s.d., standard deviation.

of patients that experienced at least one adverse event was similar in both groups (52.5 and 53.1% in the linagliptin plus pioglitazone and placebo plus pioglitazone groups, respectively). Most adverse events were of mild or moderate intensity (Table 5). Weight increase, the most frequently reported drug-related adverse event, occurred in 2.3 and 0.8% of the linagliptin plus pioglitazone and placebo plus pioglitazone arms, respectively. Hypoglycaemic events occurred in 1.2% of the linagliptin plus pioglitazone group and in none of the patients receiving placebo plus pioglitazone. The hypoglycaemic events were of mild intensity, none of which emerged while patients were receiving rescue medication and all occurred in patients aged 60 years or older.

Laboratory analyses did not reveal any clinically significant findings. Mean values for total cholesterol, HDL cholesterol and LDL cholesterol were within the normal reference range at baseline and end of treatment. Mean values for

Table 2. Adjusted means for the change from baseline at week 24 in HbA1c and FPG.

	Placebo + pioglitazone 30 mg	Linagliptin 5 mg + pioglitazone 30 mg
Number of patients, n	128	252
HbA1c (%)		
Number of patients with baseline and on-treatment results	128	252
Baseline		
Mean (s.e.)	8.58 (0.08)	8.60 (0.05)
Change from baseline		
Mean (s.e.)	−0.75 (0.11)	−1.25 (0.07)
Adjusted* mean (s.e.)	−0.56 (0.09)	−1.06 (0.06)
Comparison versus Placebo (diff. Linagliptin−Placebo)		
Adjusted* mean (s.e.)		−0.51 (0.10)
95% Confidence Interval		(−0.71, −0.30)
p-value		<0.0001
FPG (mmol/l)		
Number of patients with baseline and on-treatment results	122	243
Baseline		
Mean (s.e.)	10.4 (0.2)	10.5 (0.2)
Change from baseline		
Mean (s.e.)	−1.2 (0.2)	−2.0 (0.1)
Adjusted* mean (s.e.)	−1.0 (0.2)	−1.8 (0.1)
Comparison versus Placebo (diff. Linagliptin−Placebo)		
Adjusted* mean (s.e.)		−0.8 (0.20)
95% Confidence Interval		(−1.2, −0.4)
p-value		<0.0001

s.e., standard error.
*Model includes continuous baseline HbA1c, continuous baseline FPG, number of prior antidiabetes drugs, and treatment.

Table 3. Number of patients with categorical response at week 24.

	Placebo + pioglitazone 30 mg	Linagliptin 5 mg + pioglitazone 30 mg
Number of patients analysed, n	128	252
Number of patients with a response, n (%)		
HbA1c <7.0%	39 (30.5)	108 (42.9)
HbA1c <6.5%	18 (14.1)	44 (17.5)
HbA1c reduction from baseline ≥0.5%	65 (50.8)	189 (75.0)

triglycerides above the normal reference range were seen for linagliptin plus pioglitazone at baseline (228 mg/dl), and for placebo plus pioglitazone at baseline (236 mg/dl) and end of treatment (219 mg/dl). However, mean values decreased with respect to baseline in both groups (−35 mg/dl linagliptin plus pioglitazone; −18 mg/dl placebo plus pioglitazone). There

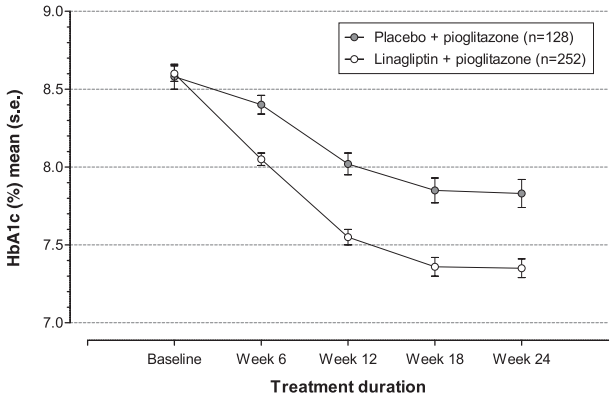

Figure 2. Non-adjusted HbA1c over time (mean ± s.e.) following treatment with linagliptin 5 mg plus pioglitazone 30 mg or placebo plus pioglitazone 30 mg for 24 weeks—full analysis set (LOCF). Differences in change from baseline in HbA1c between placebo and linagliptin were significant at each time point after baseline ($p < 0.0001$).

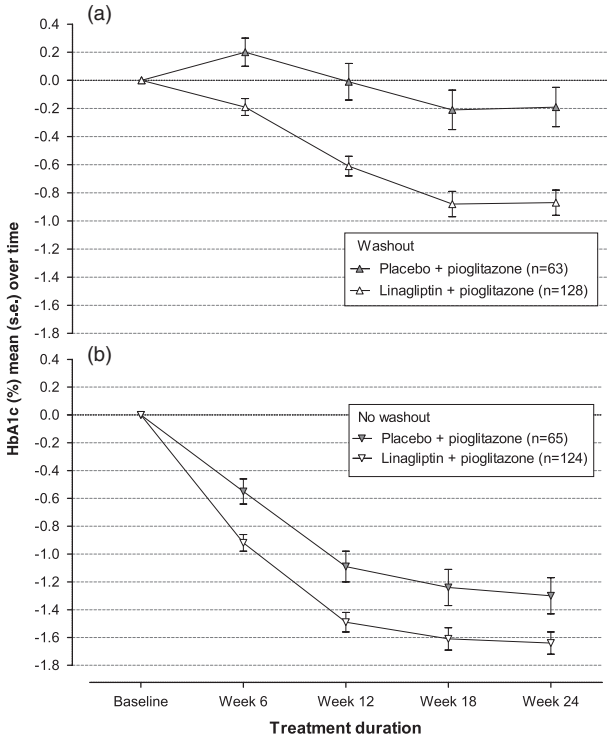

Figure 3. (a) Mean change from baseline in HbA1c following treatment with linagliptin 5 mg plus pioglitazone 30 mg or placebo plus pioglitazone 30 mg for 24 weeks for patients who had been treated with any oral antidiabetes drug and underwent washout—full analysis set (LOCF); (b) mean change from baseline in HbA1c following treatment with linagliptin 5 mg plus pioglitazone 30 mg or placebo plus pioglitazone 30 mg for 24 weeks for patients who were treatment naïve and did not require washout—FAS (LOCF).

were no clinically significant changes in renal function: 93.4 and 95.7% of patients in the linagliptin and placebo groups, respectively, continued to have normal renal function or mild renal impairment at the end of the trial.

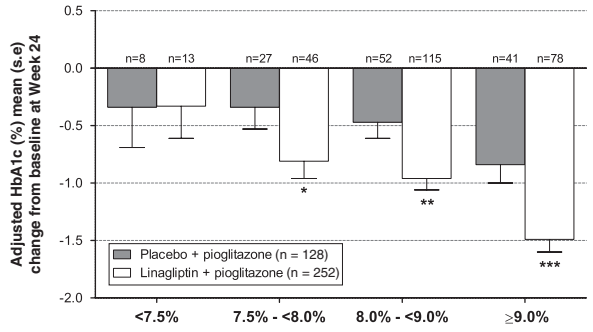

Figure 4. Adjusted mean (±s.e., plotted in one direction only, for clarity) change from baseline in HbA1c (%) by subgroups—full analysis set (LOCF). Asterisks denote statistically significant changes (*p = 0.048, **p = 0.031, ***p = 0.0008).

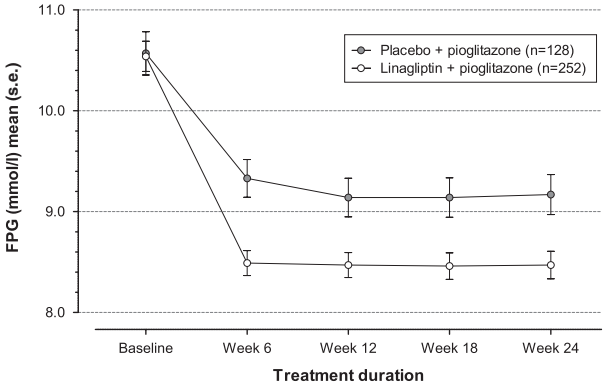

Figure 5. FPG over time (mean ± s.e.) following treatment with linagliptin 5 mg plus pioglitazone 30 mg or placebo plus pioglitazone 30 mg for 24 weeks—full analysis set (LOCF). Differences in change from baseline in FPG between placebo and linagliptin were significant at each time point after baseline (p < 0.0001).

Table 4. Adjusted mean change from baseline in fasting biomarkers and derived indices at week 24.

	Placebo + pioglitazone 30 mg	Linagliptin 5 mg + pioglitazone 30 mg
HOMA-IR [(mU/l)•(mmol/l)]		
Number of patients	80	191
Baseline, mean (s.e.)	6.01 (1.53)	5.13 (0.35)
Adjusted mean change from baseline (s.e.)	−2.58 (0.21)	−2.90 (0.14)
Comparison versus placebo		
Adjusted mean (s.e.)		−0.32 (0.23)
95% Confidence Interval		(−0.77, 0.13)
p-value		0.16
HOMA-β [(mU/l)/(mmol/l)]		
Number of patients	79	191
Baseline, mean (s.e.)	40.89 (6.11)	37.88 (3.19)
Adjusted mean change from baseline (s.e.)	−1.44 (3.89)	−2.17 (2.58)
Comparison versus placebo		
Adjusted mean (s.e.)		−0.73 (4.28)
95% Confidence Interval		(−9.16, 7.70)
p-value		0.86
Disposition index [1/((mmol/l)•(mmol/l))]		
Number of patients	96	216
Baseline, mean (s.e.)	8.56 (0.57)	7.80 (0.27)
Adjusted mean change from baseline (s.e.)	3.87 (0.93)	6.56 (0.65)
Comparison versus placebo		
Adjusted mean (s.e.)		2.69 (1.04)
95% Confidence Interval		(0.65, 4.74)
p-value		0.01

s.e., standard error.

Discussion

In this study, linagliptin 5 mg combined with pioglitazone 30 mg, both administered once daily, produced a significant, clinically meaningful and sustained improvement in glycaemic control from baseline compared with pioglitazone monotherapy (i.e. placebo plus pioglitazone). The combination of pioglitazone plus linagliptin gave an additional ~0.5% reduction in HbA1c on top of the reduction seen with pioglitazone treatment alone (1.1% HbA1c reduction for combination treatment versus 0.6% for monotherapy).

As in three other pivotal Phase III studies of linagliptin [19–21], this study showed that the clinically meaningful and sustained improvement in glycaemic control produced by linagliptin was accompanied by an enhancement of β-cell function, for example, the change in DI suggested improved β-cell responsiveness in the linagliptin plus pioglitazone group compared with those receiving pioglitazone monotherapy. However, the lack of a statistically significant difference in some indices (e.g. HOMA-β) may reflect the biological variation and the sample size in this study. In addition, the relative change in adjusted mean HOMA-IR suggested that linagliptin could have had a greater effect than placebo on this parameter, although the insulin sensitizing effects of pioglitazone could complicate assessing the effect of linagliptin, as also appears to have been the case in other trials assessing DPP-4 inhibitors in combination with gliptins [22,23].

The tolerability of linagliptin in this study was consistent with the previously reported safety profile of the drug [6,7] and no new safety concerns emerged. It is known that prolonged treatment with thiazolidinediones can cause weight gain [24] and, in this study, a small increase (1.1 kg) in body weight was seen in the linagliptin plus pioglitazone group compared with the placebo plus pioglitazone group. In general, DPP-4 inhibitors have a neutral effect on weight. However, previous findings suggest that when used in combination, DPP-4 inhibitors may elicit small increases in the weight gain induced by pioglitazone [22,23,25]. The combination of pioglitazone 30 mg/day plus vildagliptin 100 mg/day was associated with a trend toward more weight gain (2.1 kg) compared with pioglitazone monotherapy (1.4 kg) [22]. Similarly, body weight significantly increased following combination therapy with pioglitazone 30 mg/day plus sitagliptin 100 mg/day in comparison with pioglitazone monotherapy (3.0 vs. 1.9 kg; p = 0.005) [23].

Table 5. Frequency of patients with drug-related adverse events by treatment, system organ class, and preferred term.

	n (%)	
	Placebo + pioglitazone 30 mg	Linagliptin 5 mg + pioglitazone 30 mg
Number of patients	130	259
Number of patients with related AE	6 (4.6)	16 (6.2)
Gastrointestinal disorders	2 (1.5)	4 (1.5)
Abdominal pain	1 (0.8)	1 (0.4)
Constipation	1 (0.8)	2 (0.8)
Gastritis	0 (0.0)	1 (0.4)
Nausea	0 (0.0)	1 (0.4)
Vomiting	0 (0.0)	1 (0.4)
General disorders and administration site conditions	2 (1.5)	3 (1.2)
Generalized oedema	1 (0.8)	0 (0.0)
Oedema peripheral	1 (0.8)	2 (0.8)
Face oedema	0 (0.0)	1 (0.4)
Localized oedema	0 (0.0)	1 (0.4)
Investigations	1 (0.8)	6 (2.3)
Weight increased	1 (0.8)	6 (2.3)
Metabolism and nutrition disorders	2 (1.5)	5 (1.9)
Fluid retention	0 (0.0)	2 (0.8)
Hypoglycaemia	1 (0.8)	3 (1.2)
Hyperglycaemia	1 (0.8)	0 (0.0)
Hyperkalaemia	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	2 (0.8)
Headache	0 (0.0)	1 (0.4)
Hypoesthesia	0 (0.0)	1 (0.4)

Hypoglycaemia as a side effect of diabetes treatment is a major concern and some OADs, such as the insulin secretagogues, may be associated with an increase in the occurrence of hypoglycaemic events [26]. DPP-4 inhibitors generally are associated with an inherently low risk of hypoglycaemia [27] and, in this study, hypoglycaemia was rare when linagliptin was added to pioglitazone. However, hypoglycaemia incidence with linagliptin plus pioglitazone was more common than in the placebo arm, although all the events were of mild intensity. The complete absence of drug-related hypoglycaemia in the placebo arm was an unusual feature of this trial not reflected in the wider linagliptin pivotal Phase III study programme [19–21].

Dose-ranging studies indicate that the therapeutic window of linagliptin is likely to be >100-fold higher than the therapeutic dose of 5 mg [6]. In this study, when combined with pioglitazone, the adverse event rate with linagliptin was comparable to that seen with placebo, which is consistent with the other pivotal Phase III linagliptin study results [19–21]; and no clinically significant effect on lipid profiles, renal function or other laboratory measures could be ascribed to linagliptin. No severe skin disorders with linagliptin were observed.

The predominantly non-renal elimination pathway for linagliptin may mean that there is no need for dose adjustments when it is administered in patients with renal impairment. The majority of patients in this study remained with normal renal function or mild renal impairment at the end of the trial, and other studies of linagliptin in T2DM patients with severe renal impairment are ongoing.

In conclusion, the combination of linagliptin plus pioglitazone was effective and well tolerated. This may offer a valuable additive initial treatment option for T2DM patients, in particular for those unable to tolerate metformin or for those where metformin is contraindicated, such as patients with renal impairment.

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Conflict of Interest

R.-M. E., R. J., H.-J. W. and K. A. D. are employees of Boehringer Ingelheim.

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). R. G. (coordinating investigator), R.-M. E. (trial clinical monitor), H.-J. W. and K. A. D. contributed to the design of the study. R. G., R.-M. E., H.-J. W. and K. A. D. participated in data collection. R. G., R.-M. E., R. J. (trial statistician), H.-J. W. and K. A. D. participated in data analysis. All authors 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

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