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ORIGINAL ARTICLE

Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study

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Aim: To assess the efficacy and safety of adding alogliptin versus uptitrating pioglitazone in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone.

Methods: In this randomized, double-blind, active-controlled, parallel-group study, patients with type 2 diabetes and A1c ≥7.0 and ≤10.0% on metformin (≥1500 mg or maximum tolerated dose; Met) and pioglitazone 30 mg (Pio30) received alogliptin 25 mg (Alo25; n = 404) or pioglitazone 15 mg (n = 399) added to Met+Pio30 for 52 weeks. The primary endpoint was change from baseline (CFB) in A1c at weeks 26 and 52, with sequential testing for non-inferiority of Met+Pio30+Alo25 at weeks 26 and 52 and then for superiority at week 52.

Results: Met+Pio30+Alo25 showed superior glycaemic control versus Met+Pio45 at week 52 [least squares (LS) mean CFB in A1c, −0.70 vs. −0.29%; $p < 0.001$]. At week 52, Met+Pio30+Alo25 resulted in greater CFB in A1c regardless of baseline A1c ($p < 0.001$); higher proportions of patients achieving A1c ≤7.0 (33.2 vs. 21.3%) and ≤6.5% (8.7 vs. 4.3%; $p < 0.001$); greater CFB in fasting plasma glucose (FPG; LS mean CFB, −0.8 vs. −0.2 mmol/L; $p < 0.001$); and greater improvements in measures of β-cell function ($p < 0.001$). Hypoglycaemia incidence was low (Met+Pio30+Alo25, 4.5%; Met+Pio45, 1.5%), mostly mild to moderate, but with two severe events in the Met+Pio30+Alo25 group. No meaningful differences in incidences of individual adverse events were observed between treatments.

Conclusions: Adding alogliptin to an existing metformin–pioglitazone regimen provided superior glycaemic control and potentially improved β-cell function versus uptitrating pioglitazone in patients with type 2 diabetes, with no clinically important differences in safety.

Keywords: combination therapy, dipeptidylpeptidase-4, DPP-4 inhibitor, glycaemic control, metformin, pioglitazone, thiazolidinedione, triple therapy, type 2 diabetes

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Introduction

Type 2 diabetes mellitus is a chronic, progressive disease characterized primarily by insulin resistance and pancreatic β-cell failure [1]. Treatment goals aim to achieve and maintain glycaemic control to mitigate the risk of microvascular and macrovascular complications associated with this disease [2]. However, only approximately half of patients with type 2 diabetes in the United States achieve the American Diabetes Association A1c goal of <7.0%; even fewer achieve the more aggressive International Diabetes Federation goal of <6.5% [3]. Furthermore, largely due to progressive decline of β-cell function, most patients who initially achieve treatment goals eventually experience deterioration of glycaemic control [4]. Such secondary treatment failure necessitates escalation of drug doses or the use of a combination of drugs with complementary mechanisms of action to maintain glycaemic control over time.

Metformin, commonly prescribed as initial therapy for type 2 diabetes, lowers blood glucose primarily by increasing hepatic insulin sensitivity [5]. Pioglitazone, a thiazolidinedione (TZD), increases peripheral and hepatic insulin sensitivity and potentially preserves β-cell function [6,7]. Dual oral therapy with metformin and pioglitazone is a well-established treatment option for patients with type 2 diabetes [8]. Current treatment guidelines indicate that patients with inadequate glycaemic control on dual oral therapy may benefit from the addition of a third oral antidiabetic drug (OAD) before initiating insulin therapy [9,10]. For patients who have failed metformin and pioglitazone dual therapy, the addition of a dipeptidylpeptidase-4 (DPP-4) inhibitor represents an attractive treatment option. DPP-4 inhibitors inhibit the degradation of incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, thereby increasing insulin secretion and decreasing glucagon

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secretion after meals [11]. These drugs may also improve β-cell function [7]. In clinical studies, the DPP-4 inhibitor alogliptin significantly improved A1c, was weight neutral, and was associated with a low risk of hypoglycaemia and other adverse effects when administered as monotherapy or in combination with metformin, a TZD, a sulfonylurea, or insulin in patients with type 2 diabetes [12–17].

Given the distinct, but complementary mechanisms of action of alogliptin, metformin and pioglitazone, triple oral therapy with these drugs has the potential to address both insulin resistance and islet dysfunction, the core defects in type 2 diabetes. Moreover, the addition of alogliptin to an existing metformin and pioglitazone regimen versus uptitration of pioglitazone may enhance glycaemic control without the adverse effects that may be associated with maximal-dose pioglitazone. The efficacy and safety of dual oral therapy with a DPP-4 inhibitor and metformin or pioglitazone have been well documented [13–15,18–22]. In contrast, few studies have assessed the effects of triple oral therapy with these drugs [23,24]. In this study, we evaluate the efficacy and safety of adding alogliptin 25 mg versus uptitrating pioglitazone from 30 to 45 mg for 52 weeks in patients with type 2 diabetes and inadequate glycaemic control on metformin [≥1500 mg or maximum tolerated dose (MTD)] and pioglitazone 30 mg.

Methods

The protocol was approved by the institutional review board or ethics committee of each study site. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable local laws and regulations. All patients provided informed consent.

Study Population

This study included men and women with type 2 diabetes and inadequate glycaemic control defined as either (i) A1c ≥ 7.0 and ≤10.0% on metformin (1500 mg or MTD) and pioglitazone 30 mg (Met+Pio30) for at least 2 months before screening, or (b) A1c 7.5% on metformin and another OAD (excluding pioglitazone 30 or 45 mg or DPP-4 inhibitors) and subsequently A1c ≥7.0 and ≤10.0% after switching and stabilization with Met+Pio30 for 16 weeks. Eligible patients were aged 18–80 years, inclusive, with a BMI 23–45 kg/m^2, inclusive, FPG concentration <15.3 mmol/L, fasting plasma C-peptide concentration ≥0.26 nmol/L, <7 days of antidiabetic therapy (other than metformin and pioglitazone) within 2 months before screening, and systolic and diastolic blood pressure <160 and <100 mm Hg, respectively. Patients with New York Heart Association Class I–IV (European Union countries) or Class III–IV (other countries) heart failure regardless of therapy; a history of coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction within 6 months before screening; or a history or presence of any other severe disease were excluded.

Study Design

This is a 52-week, international, multicenter, randomized, double-blind, active-controlled, parallel-group, 2-arm study.

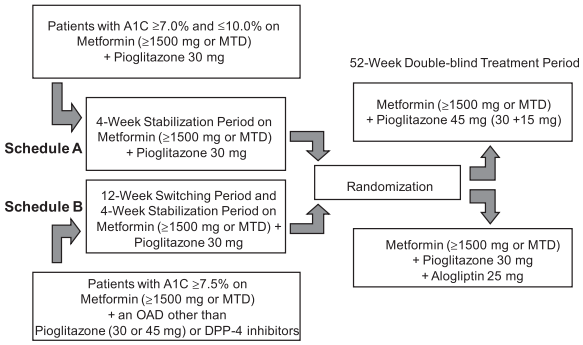

Figure 1. Study design. DPP-4, dipeptidylpeptidase-4; MTD, maximum tolerated dose; OAD, oral antidiabetic drug.

Depending on their existing OAD regimen and A1c level, patients entered the screening period by either schedule A or B (figure 1). Patients with A1c ≥7.0 and ≤10.0% on Met+Pio30 immediately entered the screening period, followed by a 4-week stabilization period on Met+Pio30 (schedule A). Patients with A1c 7.5% on metformin and another OAD entered a pre-screening period and then a 12-week switching period during which they received Met+Pio30 (schedule B). Thereafter, these patients entered the screening period and those with A1c ≥7.0 and ≤10.0% then entered the 4-week stabilization period. All eligible patients were then randomly assigned in a 1 : 1 ratio to receive either alogliptin 25 mg and pioglitazone placebo (Met+Pio30+Alo25 group) or alogliptin placebo and pioglitazone 15 mg (Met+Pio45 group), in addition to open-label Met+Pio30, during the 52-week treatment period. Patients were withdrawn from the study and received standard of care antidiabetic treatment if they met any of the following hyperglycaemic rescue criteria: (i) FPG ≥ 15.3 mmol/L after week 2 to before week 4; (ii) FPG ≥ 13.9 mmol/L from week 4 to before week 8; (iii) FPG ≥ 12.5 mmol/L from week 8 to before week 12; (iv) A1c ≥8.5% and ≤0.5% decrease from baseline in A1c at week 12 or later.

Study Endpoints

The primary efficacy endpoint was change from baseline in A1c at weeks 26 and 52. Secondary efficacy endpoints included change from baseline in A1c at all other visits; proportions of patients achieving A1c ≤7.0 and ≤6.5% at week 52; incidence of hyperglycaemic rescue; change from baseline in FPG at all visits; and changes from baseline in fasting proinsulin/insulin ratio, C-peptide, homeostasis model assessment (HOMA) β-cell function, HOMA insulin resistance, body weight, serum triglycerides, cholesterol (total, HDL, LDL) and free fatty acids at week 52. Safety variables were adverse events (AEs), clinical laboratory tests, electrocardiograms, physical examinations, vital signs and incidence of hypoglycaemia (mild to moderate hypoglycaemia: blood glucose <3.33 mmol/L with symptoms or blood glucose <2.78 mmol/L regardless of symptoms; severe hypoglycaemia: blood glucose <3.33 mmol/L and requiring assistance). Treatment-emergent AEs were defined as any AEs starting on or after the first dose and within 14 days after the last dose of double-blind study drug.

Statistical Methods

The primary analysis included all randomized patients who received at least 1 dose of double-blind study drug, had a baseline and at least 1 post-baseline A1c measurement, and had no major protocol violations (per-protocol set). Non-inferiority of Met+Pio30+Alo25 to Met+Pio45 was assessed via a planned interim analysis at week 26. Subsequently, non-inferiority and then superiority of Met+Pio30+Alo25 were assessed via a final analysis at week 52. Separate teams performed the interim analysis and final analysis; the team that performed the final analysis remained blinded to the interim data until database lock and unblinding of the final data. Non-inferiority and superiority were assessed using one-sided 97.5% CIs for the least squares (LS) mean difference in change from baseline in A1c at weeks 26 and 52 obtained from separate ANCOVA models, where study treatment, study schedule, and geographic region were class effects and baseline metformin dose and baseline A1c were continuous covariates. Non-inferiority was assessed using a margin of 0.3%. Secondary analyses included all randomized patients who received at least 1 dose of study drug and had a baseline and at least 1 post-baseline measurement (full analysis set). Secondary endpoints were analysed by ANCOVA (continuous endpoints) or nonparametric, covariance-adjusted, extended Mantel-Haenszel tests (categorical endpoints) at the two-sided 5% significance level. Changes from baseline in A1c were analysed for pre-specified subgroups based on baseline A1c (<8.0, ≥ 8.0, <9.0 and $\geq 9.0\%$), sex, age (<65, ≥ 65 and ≥ 75 years), race, ethnicity and baseline BMI (<30 and ≥ 30 kg/m^2). The last observation carried forward method was used to extrapolate missing values in all analyses. Safety assessments included all patients who received at least 1 dose of study drug.

The planned sample size of 760 patients (380 per treatment group) provided at least 90% power to declare non-inferiority in mean change from baseline in A1c at either week 26 or 52 between Met+Pio30+Alo25 and Met+Pio45 (and 80% power to declare non-inferiority at both weeks 26 and 52), assuming an s.d. of 1.1%, a non-inferiority margin of 0.3%, no difference between the treatment groups, a 0.025 one-sided significance level and inclusion of 75% of randomized patients in the per-protocol set.

Results

Patient Disposition and Baseline Characteristics

Patient disposition is shown in Figure 2. Of the 969 patients enrolled into the stabilization period, 404 were randomly assigned to receive alogliptin 25 mg (Met+Pio30+Alo25 group) and 399 to receive pioglitazone 15 mg (Met+Pio45 group) during the treatment period. More patients in the Met+Pio30+Alo25 group (283 patients; 70.0%) than the Met+Pio45 group (243 patients; 60.9%) completed the study, primarily because of a significantly higher incidence of hyperglycaemic rescue in the Met+Pio45 group [87 patients (21.8%) vs. 44 patients (10.9%); $p < 0.001$]. A total of 77 patients (19.1%) in the Met+Pio30+Alo25 group and 69 patients (17.3%) in the Met+Pio45 group discontinued the study. Demographic and baseline characteristics were generally

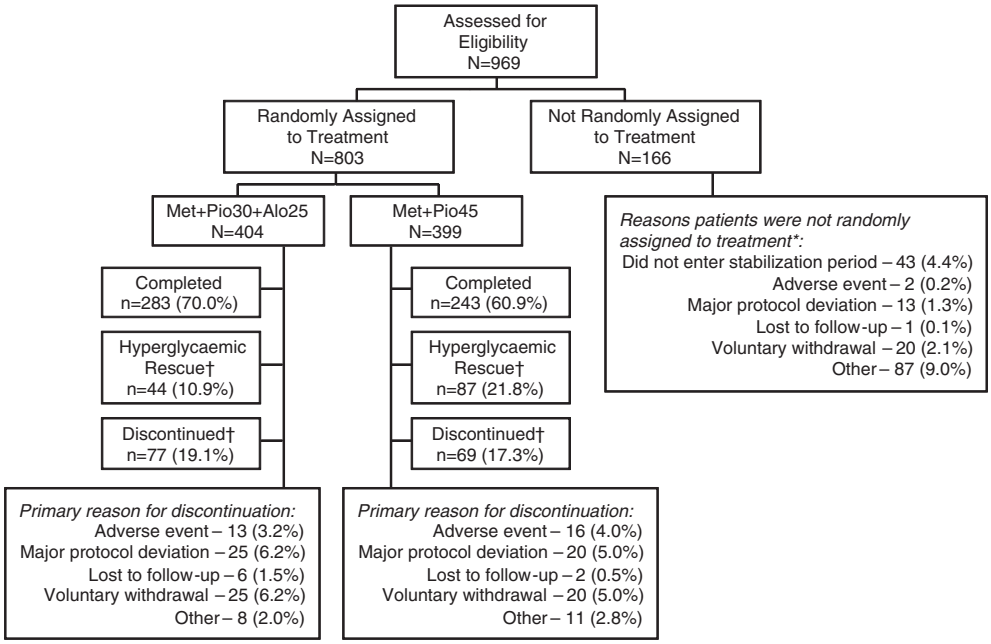

Figure 2. Disposition of patients. *Percentages are calculated based on the number of patients enrolled into the study. Reasons for not being randomly assigned to treatment are provided only for the 123 patients who entered the stabilization period; investigators were not required to record reasons for patients who failed pre-screening/screening and did not enter the stabilization period. †'Hyperglycaemic Rescue' and 'Discontinued' were mutually exclusive groups. Hyperglycaemic rescue criteria as a result of lack of efficacy were based on fasting plasma glucose levels from week 2 to before week 12, and A1c levels at week 12 or later. Alo, Alogliptin 25 mg; Met, metformin $\geq$ 1500 mg or maximum tolerated dose; Pio30, pioglitazone 30 mg; Pio45, pioglitazone 45 mg.

Table 1. Patient demographic and baseline characteristics.

Characteristics	Met+Pio30+Alo25 $N = 404$*	Met+Pio45 $N = 399$*
Age (year), mean (s.d.)	54.3 (9.86)	55.9 (9.94)
Gender, n (%)		
Male	210 (52.0)	204 (51.1)
Female	194 (48.0)	195 (48.9)
Race, n (%)		
White	242 (59.9)	256 (64.2)
Asian	79 (19.6)	78 (19.5)
African American	41 (10.1)	36 (9.0)
Other	42 (10.4)	29 (7.3)
Ethnicity, n (%)		
Hispanic or Latino	30 (7.4)	31 (7.8)
Non Hispanic or Latino	374 (92.6)	368 (92.2)
Weight (kg), mean (s.d.)	88.2 (18.90)	88.0 (19.28)
BMI (kg/m^2), mean (s.d.)	31.5 (5.25)	31.6 (5.18)
Diabetes duration (year), mean (s.d.)	7.5 (5.24)	6.9 (4.61)
Daily metformin use (mg), median (range)	1700 (500–3400)	1700 (500–3000)
A1c (%), mean (s.d.)	n = 303†	n = 306†
	8.3 (0.82)	8.1 (0.83)
	n = 397‡	n = 394‡
	8.2 (0.86)	8.1 (0.83)
FPG (mmol/L), mean (s.d.)	n = 399‡	n = 396‡
	9.0 (2.32)	9.0 (2.37)

Alo25, alogliptin 25 mg; FPG, fasting plasma glucose; Met, metformin ≥1500 mg or maximum tolerated dose; Pio30, pioglitazone 30 mg; Pio45, pioglitazone 45 mg.
*N = all subjects who were randomly assigned to receive double-blind study drug (randomized set).
†n = all randomly assigned patients who received at least 1 dose of double-blind study drug, had a baseline and at least 1 post-baseline A1c measurement, and had no major protocol violations (per-protocol set).
‡n = all randomly assigned patients who received at least 1 dose of double-blind study drug and had a baseline and at least 1 post-baseline measurement (full analysis set).

similar between the treatment groups (Table 1). The majority of patients (62.0%) were White and approximately half (51.6%) were male. The patients had a mean age of 55.1 years, BMI of 31.6 kg/m^2 and duration of diabetes of 7.2 years. Median baseline metformin use was 1700 mg per day.

Efficacy

The mean A1c level at baseline was 8.3% in the Met+Pio30+Alo25 group and 8.1% in the Met+Pio45 group (Table 1; per-protocol set). At weeks 26 and 52, significantly ($p < 0.001$) greater decreases from baseline in A1c were observed in the Met+Pio30+Alo25 group (LS mean change, −0.89% and −0.70%, respectively) compared with the Met+Pio45 group (−0.42 and −0.29%, respectively) (figure 3A; per-protocol set). The decreases observed in the Met+Pio30+Alo25 group were non-inferior at weeks 26 and 52 and superior at week 52 to those observed in the Met+Pio45 group. The LS mean differences in change from baseline in A1c between the treatment groups and the corresponding one-sided 97.5% CIs were −0.47% (−∞, −0.35%) at week 26 and −0.42% (−∞, −0.28%) at week 52. Similar results were obtained when the primary analysis was performed using the full analysis set. A significantly ($p < 0.001$) greater decrease from baseline in A1c was observed in the Met+Pio30+Alo25 group at each study visit compared with the Met+Pio45 group (figure 3A); however, both treatment groups showed a trend toward a slight and progressive increase in HbA1c following week 20. Furthermore, at week 52, the proportions of patients achieving A1c levels ≤7.0 and ≤6.5% were significantly ($p < 0.001$) higher in the Met+Pio30+Alo25 group than in the Met+Pio45 group (figure 3B).

Significantly ($p < 0.005$) greater LS mean decreases from baseline in A1c were observed in the Met+Pio30+Alo25 group compared with the Met+Pio45 group at week 52, regardless of baseline A1c (Table 2). In addition, clinically meaningful decreases in A1c were observed in both treatment groups across subgroups of sex, age, race, ethnicity, and baseline BMI at week 52; the mean decreases from baseline in A1c were generally greater in the Met+Pio30+Alo25 group than in the Met+Pio45 group for all subgroups tested.

The mean FPG level at baseline was 9.0 mmol/L in both treatment groups (Table 1; full analysis set). At all study visits, significantly ($p < 0.01$) greater decreases from baseline in FPG were observed in the Met+Pio30+Alo25 group compared with the Met+Pio45 group (figure 3C). At weeks 26 and 52, the LS mean changes from baseline were −0.9 and −0.8 mmol/L, respectively, for the Met+Pio30+Alo25 group and −0.3 and −0.2 mmol/L, respectively, for the Met+Pio45 group.

Proinsulin/insulin ratio and HOMA β-cell function were significantly ($p < 0.001$) improved in the Met+Pio30+Alo25 group compared with the Met+Pio45 group at week 52 (Table 2). However, no statistically significant differences in LS mean change from baseline in C-peptide and HOMA insulin resistance were observed between the treatment groups at week 52. In addition, at week 52, no statistically significant differences in LS mean change from baseline in body weight, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides or free fatty acids were observed between the treatment groups (Table 2).

Safety and Tolerability

A total of 289 patients (71.5%) in the Met+Pio30+Alo25 group and 275 patients (68.9%) in the Met+Pio45 group experienced at least 1 treatment-emergent AE (Table 3). The most common AEs, experienced by ≥5% of patients in either treatment group, were upper respiratory tract infection, nasopharyngitis, hypertension, urinary tract infection, influenza and diarrhoea (Table 3). Incidences of individual AEs were generally similar between the treatment groups, with no clinically meaningful differences observed.

A total of 88 patients (21.8%) in the Met+Pio30+Alo25 group and 75 patients (18.8%) in the Met+Pio45 group experienced drug-related AEs. The most common drug-related AE was peripheral oedema, experienced by 8 patients (2.0%) in the Met+Pio30+Alo25 group and 12 patients (3.0%) in the Met+Pio45 group. The majority of AEs were mild or moderate in intensity; 24 patients (5.9%) in the Met+Pio30+Alo25 group

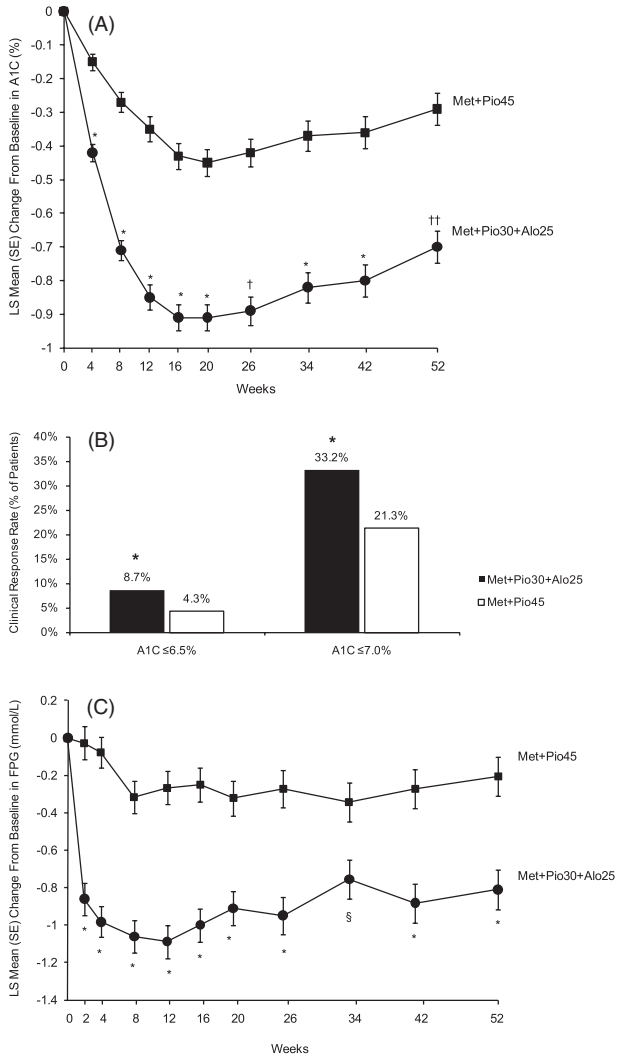

Figure 3. Least squares (LS) mean (±s.e.) change from baseline in A1c over the 52-week treatment period (A); clinical response rate (% of patients) at week 52 (B); and LS mean (±s.e.) change from baseline in fasting plasma glucose (FPG) over the 52-week treatment period (C). *$p < 0.001$ versus Met+Pio45 from an ANCOVA (A1c and FPG) or an extended Mantel–Haenszel test (clinical response rate). †LS mean difference (one-sided 97.5% CI) = −0.47 (−∞, −0.35), indicating the mean change from baseline in A1c observed in the Met+Pio30+Alo25 group was non-inferior to that in the Met+Pio45 group. ††LS mean difference (one-sided 97.5% CI) = −0.42 (−∞, −0.28), indicating the mean change from baseline in A1c observed in the Met+Pio30+Alo25 group was non-inferior and superior to that in the Met+Pio45 group. §$p = 0.005$ versus Met+Pio45 from an ANCOVA. Alo, Alogliptin 25 mg; Met, metformin ≥1500 mg or maximum tolerated dose; Pio30, pioglitazone 30 mg; Pio45, pioglitazone 45 mg.

and 27 patients (6.8%) in the Met+Pio45 group experienced at least 1 severe AE.

The proportions of patients who experienced at least 1 AE that led to study drug discontinuation or at least 1 serious adverse event (SAE) were similar between treatment groups (Table 3). Three patients in the Met+Pio45 group experienced an SAE considered related to study drug (myocardial infarction, unstable angina and hypotension). One death was reported in the Met+Pio30+Alo25 group (because of myocardial infarction, considered not drug related).

No new safety issues were observed with respect to AEs of special interest for patients with type 2 diabetes and the study drugs. A higher proportion of patients in the Met+Pio30+Alo25 group (21 patients; 5.2%) compared with the Met+Pio45 group (9 patients; 2.3%) experienced drug-related skin and subcutaneous disorders, the most common being pruritus [5 patients (1.2%) vs. 3 patients (0.8%)] and rash [5 patients (1.2%) vs. 2 patients (0.5%)]. Two patients (Met+Pio30+Alo25 group) discontinued study drug because of AEs of pruritic rash and generalized rash, both of which resolved. No meaningful differences were observed between the Met+Pio30+Alo25 and Met+Pio45 groups in the incidence of major adverse cardiac events (including cardiovascular death, myocardial infarction and stroke) [2 patients (0.5%) vs. 3 patients (0.8%)], cardiac failure [2 patients (0.5%) vs. 1 patient (0.3%)], or bone fractures [6 patients (1.5%) vs. 4 patients (1.0%)]. Hypoglycaemia was experienced by 18 patients (4.5%) in the Met+Pio30+Alo25 group and 6 patients (1.5%) in the Met+Pio45 group. Most hypoglycaemic events were mild to moderate; 2 events in the Met+Pio30+Alo25 group were severe.

No clinically meaningful differences were observed between the treatment groups for clinical laboratory, electrocardiographic, physical examination, or vital sign results.

Discussion

This study is the first to evaluate the efficacy and safety of adding a DPP-4 inhibitor to a submaximal dose of a TZD versus uptitrating the TZD dose in patients with type 2 diabetes who have failed metformin and TZD dual therapy. Adding alogliptin to an existing metformin and pioglitazone regimen (triple oral therapy) in patients with inadequate glycaemic control provided clinically relevant and superior improvement in A1c compared with uptitrating pioglitazone (dual oral therapy) after 52 weeks of treatment, without increasing safety or tolerability concerns. In addition, after 26 weeks of treatment, the improvement in A1c observed with triple therapy was non-inferior to that observed with dual therapy. Triple therapy also led to significantly greater improvements in FPG at weeks 26 and 52 compared with dual therapy. The glycaemic benefits of triple therapy were observed as early as week 4 and maintained throughout the 52-week treatment period. Nonetheless, both dual and triple therapy showed a slight and progressive trend toward increasing HbA1c following week 20.

Consistent with the observed superior glycaemic control, triple therapy resulted in significantly greater proportions of patients achieving A1c levels ≤6.5 and ≤7.0% and a lower incidence of hyperglycaemic rescue at week 52. As shown with other antidiabetic regimens [25], patients with higher baseline A1c experienced greater A1c improvements in this study. Furthermore, clinically relevant improvements in A1c were observed with triple therapy regardless of age, sex, ethnicity, race and baseline BMI, showing the efficacy of this treatment option in a variety of patients with type 2 diabetes.

Table 2. Secondary efficacy variables: changes from baseline to week 52.

Variable	Met+Pio30+Alo25 *N* = 404	Met+Pio45 *N* = 399	p value*
A1c (%)			
Baseline A1c < 8.0%	n = 119	n = 146	
Week 52 ΔBL			
LS mean (s.e.)	−0.31 (0.068)	−0.05 (0.061)	
LS mean difference (95% CI)		−0.26 (−0.45, −0.08)	0.004
Baseline A1c ≥ 8.0%	n = 184	n = 160	
Week 52 ΔBL			
LS mean (s.e.)	−0.99 (0.067)	−0.46 (0.071)	
LS mean difference (95% CI)		−0.53 (−0.72, −0.34)	<0.001
Baseline A1c < 9.0%	n = 238	n = 248	
Week 52 ΔBL			
LS mean (s.e.)	−0.53 (0.049)	−0.23 (0.048)	
LS mean difference (95% CI)		−0.30 (−0.43, −0.16)	<0.001
Baseline A1c ≥ 9.0%	n = 65	n = 58	
Week 52 ΔBL			
LS mean (s.e.)	−1.37 (0.131)	−0.48 (0.138)	
LS mean difference (95% CI)		−0.90 (−1.28, −0.52)	<0.001
Proinsulin/insulin ratio	n = 381	n = 375	
Baseline			
Mean (s.d.)	0.294 (0.2113)	0.297 (0.2148)	
Week 52 ΔBL			
LS mean (s.e.)	−0.048 (0.0080)	−0.007 (0.0081)	
LS mean difference (95% CI)		−0.041 (−0.063, −0.018)	<0.001
C-peptide (nmol/L)	n = 395	n = 390	
Baseline			
Mean (s.d.)	0.71 (0.307)	0.72 (0.361)	
Week 52 ΔBL			
LS mean (s.e.)	0.06 (0.014)	0.04 (0.014)	
LS mean difference (95% CI)		0.02 (−0.016, 0.064)	0.230
HOMA β-cell function	n = 381	n = 377	
Baseline			
Mean (s.d.)	47.92 (44.951)	57.59 (193.876)	
Week 52 ΔBL			
LS mean (s.e.)	15.02 (2.740)	2.06 (2.754)	
LS mean difference (95% CI)		12.96 (5.33, 20.59)	<0.001
HOMA insulin resistance	n = 381	n = 378	
Baseline			
Mean (s.d.)	4.34 (3.288)	4.46 (4.317)	
Week 52 ΔBL			
LS mean (s.e.)	0.35 (0.231)	0.54 (0.232)	
LS mean difference (95% CI)		−0.19 (−0.83, 0.46)	0.567
Weight (kg)	n = 395	n = 394	
Baseline			
Mean (s.d.)	87.90 (18.424)	88.46 (19.231)	
Week 52 ΔBL			
LS mean (s.e.)	1.10 (0.194)	1.60 (0.194)	
LS mean difference (95% CI)		−0.50 (−0.13, 0.04)	0.071
Total cholesterol (mmol/L)	n = 399	n = 395	
Baseline			
Mean (s.d.)	5.02 (1.154)	5.05 (1.132)	
Week 52 ΔBL			
LS mean (s.e.)	−0.11 (0.041)	0.00 (0.041)	
LS mean difference (95% CI)		−0.11 (−0.22, 0.00)	0.058
HDL cholesterol (mmol/L)	n = 399	n = 39	
Baseline			
Mean (s.d.)	1.30 (0.294)	1.29 (0.335)	
Week 52 ΔBL			
LS mean (s.e.)	−0.01 (0.010)	0.01 (0.010)	
LS mean difference (95% CI)		−0.02 (−0.04, 0.01)	0.228

Table 2. Continued.

Variable	Met+Pio30+Alo25 *N* = 404	Met+Pio45 *N* = 399	p value*
LDL cholesterol (mmol/L)	n = 390	n = 386	
Baseline			
Mean (s.d.)	2.88 (0.978)	2.89 (0.935)	
Week 52 ΔBL			
LS mean (s.e.)	−0.05 (0.034)	0.03 (0.034)	
LS mean difference (95% CI)		−0.07 (−0.17, 0.02)	0.132
Triglycerides (mmol/L)	n = 399	n = 395	
Baseline			
Mean (s.d.)	1.84 (1.350)	1.95 (1.317)	
Week 52 ΔBL			
LS mean (s.e.)	−0.18 (0.039)	−0.09 (0.039)	
LS mean difference (95% CI)		−0.10 (−0.20, 0.01)	0.080
Free fatty acids (mmol/L)	n = 367	n = 368	
Baseline			
Mean (s.d.)	0.5746 (0.24149)	0.5547 (0.21330)	
Week 52 ΔBL			
LS mean (s.e.)	−0.0294 (0.01173)	0.0019 (0.01171)	
LS mean difference (95% CI)		−0.0314 (−0.0640, 0.0012)	0.059

Alo25, alogliptin 25 mg; CI, confidence interval; ΔBL, change from baseline; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; LS, least squares; Met, metformin ≥1500 mg or maximum tolerated dose; Pio30, pioglitazone 30 mg; Pio45, pioglitazone 45 mg.
*p values and corresponding 95% CIs are for testing the equality of the mean response in the Met+Pio30+Alo25 group to the mean response in the Met+Pio45 group.

Table 3. Summary of patients with treatment-emergent adverse events.

Variable	Met+Pio30+Alo25 *N* = 404 n (%)	Met+Pio45 *N* = 399 n (%)
AEs	289 (71.5)	275 (68.9)
AEs leading to discontinuation*	12 (3.0)	16 (4.0)
SAEs	20 (5.0)	20 (5.0)
Deaths	1 (0.2)	0
AEs experienced by ≥3% patients in either treatment group†		
Upper respiratory tract infection	29 (7.2)	16 (4.0)
Nasopharyngitis	28 (6.9)	21 (5.3)
Hypertension	24 (5.9)	22 (5.5)
Urinary tract infection	22 (5.4)	13 (3.3)
Bronchitis	19 (4.7)	12 (3.0)
Headache	19 (4.7)	16 (4.0)
Influenza	18 (4.5)	23 (5.8)
Dyslipidaemia	18 (4.5)	18 (4.5)
Oedema peripheral	16 (4.0)	18 (4.5)
Back pain	15 (3.7)	17 (4.3)
Arthralgia	13 (3.2)	13 (3.3)
Neutropenia	12 (3.0)	19 (4.8)
Anaemia	12 (3.0)	18 (4.5)
Diarrhoea	11 (2.7)	24 (6.0)
Hypoglycaemia	18 (4.5)	6 (1.5)
Mild to moderate	16 (4.0)	6 (1.5)
Severe	2 (0.5)	0

AEs, adverse events; Alo25, alogliptin 25 mg; Met, metformin ≥1500 mg or maximum tolerated dose; Pio30, pioglitazone 30 mg; Pio45, pioglitazone 45 mg; SAEs, serious adverse events.
*Adverse events leading to permanent or temporary discontinuation of study drug.
†AEs are presented in order of decreasing incidence in the Met+Pio30 +Alo25 group.

A key pathogenetic determinant underlying the deterioration of glycaemic control in patients with type 2 diabetes is the progressive decline in β-cell function [1,7]. Evidence suggests that both TZDs and DPP-4 inhibitors may improve β-cell function [7]. In this study, proinsulin/insulin ratio and HOMA β-cell function were significantly increased with triple therapy at week 52, suggesting that the addition of alogliptin may improve residual β-cell function compared with uptitration of pioglitazone in patients who have failed metformin and pioglitazone dual therapy. Certainly, this could be expected based on the secretagogue properties of alogliptin given as third agent in comparison with uptitration of pioglitazone that does not directly act on β-cell function.

Nonetheless, further studies are required to show how long preservation or even recovery of β-cell function with triple therapy may last. No difference in change from baseline in HOMA insulin resistance was observed between the treatments.

In clinical studies, pioglitazone treatment has been associated with weight gain, increased HDL cholesterol levels and decreased triglyceride levels, with little or no difference between the 30 and 45 mg doses [6]. In contrast, alogliptin has shown no clinically meaningful effect on body weight or lipid variables [12–17]. Consistent with these observations, in the current study, the changes from baseline in body weight and lipid variables at week 52 were similar between triple and dual therapy.

In this study, adding alogliptin was generally well tolerated, with no clinically important safety differences between the treatment groups. The incidences of SAEs and AEs leading to study drug discontinuation were similar between triple and dual therapy. No new safety issues were observed with

regards to AEs of special interest for patients with type 2 diabetes or the study drugs, including major adverse cardiac events, cardiac failure, peripheral oedema and bone fracture. The higher incidence of skin-related AEs, primarily pruritus and rash, observed with triple therapy is consistent with data from other clinical studies with alogliptin [12, 13]. Despite the improved glycaemic control observed with triple therapy, the incidence of hypoglycaemia was low, although two cases of severe hypoglycaemia were observed in patients randomized to the Alogliptin arm versus none on the comparator group. In clinical studies, alogliptin has been associated with a low risk of hypoglycaemia, with no or very few cases of severe hypoglycaemia [13–17], similar to what experienced with other DPP-4 inhibitors [19, 20, 22] and consistent with its glucose-dependent mechanism of action [11].

The beneficial effects and favourable safety profile of triple oral therapy with alogliptin observed in the current study are consistent with the results of a recent study in which the addition of alogliptin and pioglitazone for 26 weeks led to greater decreases in A1c than the addition of pioglitazone alone in patients with type 2 diabetes and inadequate glycaemic control on metformin [23]. Similar beneficial effects of triple oral therapy with a DPP-4 inhibitor were observed in another recent study comparing the effects of sitagliptin with placebo after 18 weeks of treatment in patients with inadequate glycaemic control on metformin and rosiglitazone dual therapy [24].

A potential limitation of the current study is that the combined effects of three OADs were compared with those of only two OADs. In clinical practice, when patients fail treatment with a combination of metformin and pioglitazone at the most commonly used pioglitazone dose of 30 mg, treatment options include increasing the pioglitazone dose to 45 mg, adding a third OAD such as a DPP-4 inhibitor or sulfonylurea, or adding insulin. This study was specifically designed to compare the option of maximizing the pioglitazone dose, which addresses primarily insulin resistance, to introducing a DPP-4 inhibitor, which has a complementary mechanism of action that addresses islet dysfunction, in patients who were failing treatment with two insulin-sensitizing drugs. Future studies should evaluate the potential benefits of triple therapy with a DPP-4 inhibitor in terms of weight gain, hypoglycaemia, compliance and overall tolerability compared with triple therapy with another agent, such as a sulfonylurea or insulin.

The current study highlights the value of triple oral therapy with drugs with distinct, but complementary mechanisms of action that target the underlying core defects in type 2 diabetes, insulin resistance and islet dysfunction. It also supports the introduction of a DPP-4 inhibitor as a third OAD earlier in the treatment algorithm, rather than increasing the pioglitazone dose, for patients who are failing metformin and pioglitazone dual therapy.

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Conflict of Interest

E. B. has received clinical trial funding from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Lorenz Biotech, Medtronic, Merck Sharp & Dohme, Novartis, NovoNordisk, Roche, Sanofi-Aventis and Takeda; research support from Novartis and GlaxoSmithKline; advisory board fees from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Novartis and Roche; and lecture fees from AstraZeneca, Berlin Chemie, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Lorenz Biotech, Medtronic, Novartis, NovoNordisk, Roche and Sanofi-Aventis. G. C. E. has received honoraria from Servier Laboratories, Novartis, and Sanofi-Aventis. C. A. W. and P. R. F. are employees of Takeda Global Research & Development Center, Inc., and have declared that they have no other conflict of interest.

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