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Editor's Choice

Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study

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Disclosures
Professor Michael Nauck has received honoraria from Takeda for serving on advisory boards and presenting data on alogliptin treatment. Professor Nauck has also received honoraria from Merck & Co., Bristol-Myers Squibb, GlaxoSmithKline, Merck (Darmstadt), Novartis, Probiodrug and Roche for similar activities concerning other DPP-4 inhibitors. Dr Graham Ellis has received honoraria from Novartis, South Africa for serving on their vildagliptin advisory board. The remaining authors are employed by Takeda Global Research & Development Center, Inc., the company that funded this study and manufacturer of alogliptin (see affiliations).

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SUMMARY

Aims: To evaluate the efficacy and safety of alogliptin, a new dipeptidyl peptidase-4 inhibitor, for 26 weeks at once-daily doses of 12.5 and 25 mg in combination with metformin in patients whose HbA_{1c} levels were inadequately controlled on metformin alone. **Methods and patients:** Patients with type 2 diabetes and inadequate glycaemic control (HbA_{1c} 7.0-10.0%) were randomised to continue a stable daily metformin dose regimen (≥ 1500 mg) plus the addition of placebo (n = 104) or alogliptin at once-daily doses of 12.5 (n = 213) or 25 mg (n = 210). HbA_{1c}, insulin, proinsulin, C-peptide and fasting plasma glucose (FPG) concentrations were determined over a period of 26 weeks. **Results:** Alogliptin at either dose produced least squares mean (SE) decreases from baseline in HbA_{1c} of −0.6 (0.1)% and in FPG of −17.0 (2.5) mg/dl [−1.0 (0.1) mmol/l], decreases that were significantly ($p < 0.001$) greater than those observed with placebo. The between treatment differences (alogliptin − placebo) in FPG reached statistical significance ($p < 0.001$) as early as week 1 and persisted for the duration of the study. Overall, adverse events (AEs) observed with alogliptin were not substantially different from those observed with placebo. This includes low event rates for gastrointestinal side effects and hypoglycaemic episodes. There was no dose-related pattern of AE reporting between alogliptin groups and few serious AEs were reported. **Conclusion:** Alogliptin is an effective and safe treatment for type 2 diabetes when added to metformin for patients not sufficiently controlled on metformin monotherapy.

What's known
- Metformin is the most commonly prescribed first-line drug worldwide for the treatment of type 2 diabetes.
- However, metformin monotherapy may fail to maintain glucose control over time, largely because of the progressive loss of beta-cell function in patients with type 2 diabetes.

What's new
- Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a new class of antihyperglycaemic agents for use as monotherapy and add-on therapy with other agents, including metformin.
- This study evaluates the efficacy and safety of alogliptin, a new DPP-4 inhibitor, for 26 weeks at once-daily doses of 12.5 and 25 mg in combination with metformin in patients whose HbA_{1c} levels were inadequately controlled on metformin alone.

Introduction

Alogliptin is a potent, highly selective (1), orally available inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. DPP-4 is thought to be primarily responsible for the *in vivo* degradation of two incretin hormones released in response to nutrient ingestion (2), namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Both peptide hormones exert important effects on islet beta cells to stimulate glucose-dependent insulin secretion as well as to stimulate proliferation and inhibit apoptosis of beta cell (3–5). GLP-1 also suppresses glucagon secretion from pancreatic alpha cells, delays gastric emptying and reduces food intake (4,6). The glucose-lowering actions of GLP-1, but not GIP, are relatively well preserved in patients with type 2 diabetes mellitus (2,5,7).

Metformin is the most commonly prescribed first-line drug worldwide for the treatment of type 2 diabetes; it acts by decreasing both hepatic glucose production and intestinal glucose absorption, while improving insulin sensitivity (8). Metformin monotherapy may, however, fail to maintain glucose control over time, largely because of the progressive loss of beta-cell function in patients with type 2 diabetes (9,10). While other classes of antihyperglycaemic agents have been used successfully

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in combination with metformin when metformin alone fails to maintain glycaemic control, side effects of weight gain and hypoglycaemia are commonly observed (11,12).

In response to the globally rising incidence and burden of type 2 diabetes (13) and to the limitations of the currently available treatments for glycaemic control, DPP-4 inhibitors have emerged as a new class of antihyperglycaemic agents for use as monotherapy and add-on therapy with other agents, including metformin. Inhibition of DPP-4 with sitagliptin and vildagliptin has been shown to improve glycaemic control in patients with type 2 diabetes by inhibiting the degradation of GLP-1 and GIP (11,14,15). Given their complementary mechanisms of action, the addition of DPP-4 inhibitors, such as alogliptin, to ongoing metformin therapy may provide synergistic glycaemic control. The aim of this study was to evaluate the efficacy and safety over 26 weeks of alogliptin at once-daily doses of 12.5 and 25 mg compared with placebo in combination with metformin in patients whose HbA_{1c} levels were inadequately controlled on metformin alone.

Patients and methods

Patients

This study was conducted in accordance with the requirements of the International Conference on Harmonisation Guideline for Good Clinical Practice E6, the World Medical Association Declaration of Helsinki and local requirements of each participating region. The institutional review board or ethics committee for each study site approved the final protocol and informed consent form. Before undergoing any study procedures, patients were required to provide written, informed consent.

Study participants were men and women (aged 18-80 years) with an historical diagnosis of type 2 diabetes mellitus and inadequate glycaemic control (HbA_{1c} between 7.0% and 10.0%) despite an ongoing (≥ 3 months) stable metformin monotherapy regimen (≥ 1500 mg per day for at least 8 weeks). Inclusion criteria also included a body mass index (BMI) between 23 and 45 kg/m^2; a C-peptide concentration ≥ 0.26 nmol/l (0.8 ng/ml) and serum creatinine < 1.5 mg/dl (men) or < 1.4 mg/dl (women). Additional inclusion criteria to be satisfied at the completion of the run-in/stabilisation period included HbA_{1c} between 7.0% and 10.0%, fasting plasma glucose (FPG) < 275 mg/dl (< 15.3 mmol/l) and ≥ 75% compliance with the single-blind placebo regimen.

Patients who had used antidiabetic agents other than metformin within the 3 months prior to screening were excluded. Patients with a urine albumin/creatinine ratio ≥ 113 mg/mol (≥ 1000 mg/g); a history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years); laser treatment for proliferative diabetic retinopathy within 6 months; a history of treated diabetic gastroparesis; New York Heart Association Class III or IV heart failure; or history of coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction within 6 months were also excluded. The use of oral or systemically injected glucocorticoids (exempted was the use of inhaled corticosteroids) or the use of weight-loss drugs within the 3 months prior to randomisation was prohibited.

Study design

This was a 26-week, randomised, double-blind, placebo-controlled clinical trial conducted at 115 sites in 15 countries. The study comprised a 2-week screening period, a 4-week run-in/stabilisation period, a 26-week treatment period and a 2-week follow-up period. At the start of the run-in/stabilisation period, eligible patients were switched from their own metformin medication to open-label treatment with an equivalent dose of a generic, immediate-release metformin formulation (≥ 1500 mg daily dose, excepting those patients with documentation at screening indicating intolerance to this dose, whereupon the patient's maximum tolerated dose of metformin was used). In addition to metformin, patients received placebo for alogliptin in a single-blind fashion during the stabilisation period. Once established, the metformin dose was kept unchanged for the remainder of the stabilisation period and throughout the study. After completion of the 4-week stabilisation period, patients who continued to satisfy the eligibility requirements were randomised 2 : 2 : 1 via an interactive voice response system to 26 weeks of double-blind treatment with either alogliptin 12.5 mg plus metformin, alogliptin 25 mg plus metformin or placebo plus metformin using a permuted block schedule stratified for HbA_{1c} at week 1 (HbA_{1c} < 8.0% vs. ≥ 8.0%) and geographical region.

Patients requiring hyperglycaemia rescue during the 26-week treatment period were terminated from the study. Rescue therapy for hyperglycaemia was initiated if FPG was ≥ 275 mg/dl (≥ 15.3 mmol/l) after more than 1 week of treatment but prior to the week 4 visit; if FPG was ≥ 250 mg/dl (≥ 13.9 mmol/l) after week 4 but prior to week 8; if FPG was ≥ 225 mg/dl (≥ 12.5 mmol/l) after week 8 but prior to week 12; or if HbA_{1c} was ≥ 8.5% with ≤ 0.5% reduction in HbA_{1c} compared with baseline after week 12 through

the end-of-treatment visit. FPG results meeting these criteria were confirmed by retest.

Assessments

Patients were required to fast overnight for ≥ 8 h prior to each scheduled visit during the 26-week treatment period. Visits included assessment of vital signs, physical examination, concomitant medication review and adverse event (AE) monitoring, review of diaries and glucometer readings, laboratory assessments (haematology, serum chemistry and urinalysis) and documentation of drug dosing compliance, as determined by via pill count. HbA_{1c}, insulin, proinsulin and C-peptide were assessed at baseline and at every visit from week 4 to week 26. FPG was assessed at baseline and at every visit from week 1 to week 26. Clinical examinations, assessment of vital signs, concomitant medication review and AE monitoring were performed during the follow-up visit (week 28).

Statistical analysis

A planned sample size of 500 patients was considered sufficient to detect a treatment-group difference (either alogliptin dose vs. placebo) in HbA_{1c} change from baseline as small as 0.4% with 95% power using a two-sample *t*-test. This calculation assumed a standard deviation of 0.8%, a two-sided 0.05 significance level and at least 80% of randomised patients being evaluable for analysis.

All efficacy analyses were based on the full analysis set (FAS), defined as all patients receiving randomised treatment assignment via interactive voice response system. For a particular variable, the FAS included all patients who had a baseline assessment and at least one postbaseline efficacy assessment. The safety set included all patients who took at least one dose of double-blind study drug.

The primary efficacy end-point was change in HbA_{1c} from baseline to week 26. Secondary efficacy end-points included change from baseline to intermediate time points in HbA_{1c}; change from baseline in FPG; incidence of marked hyperglycaemia [FPG ≥ 200 mg/dl (≥ 11.1 mmol/l)] and hyperglycaemic rescue; changes from baseline in fasting C-peptide, proinsulin, insulin and proinsulin/insulin ratio; clinical response, as measured by the incidence of HbA_{1c} ≤ 6.5% or ≤ 7.0% and incidence of HbA_{1c} decrease from baseline ≥ 0.5% or ≥ 1.0% at week 26; and change from baseline in body weight.

The primary efficacy analysis used an ANCOVA model to evaluate treatment effect through comparison of each active dose plus metformin to placebo plus metformin. The model included study treatment and geographical region as class variables and baseline metformin dose and baseline HbA_{1c} as continuous covariates. Starting with the alogliptin 25 mg dose, the treatment effect was evaluated at the 0.05 significance level using a contrast derived from the primary analysis model; if significant, the 12.5 mg dose treatment effect was evaluated analogously in a step-down fashion. For the primary and secondary analyses, the last-observation-carried-forward method was used to impute missing data.

Although no formal statistical hypothesis testing was performed, subgroup analyses of change from baseline in HbA_{1c} were conducted for subgroups defined by gender, age, race, Hispanic ethnicity and baseline BMI. All secondary continuous variables were analysed at each visit using the primary model as specified for the analysis of HbA_{1c}, but with the corresponding baseline value modelled as a covariate.

The incidence variables (clinical response variables, hyperglycaemia incidence and rescue incidence) were summarised by percentage and frequency for each treatment group; treatment comparisons were performed using non-parametric, covariance-adjusted extended Mantel-Haenszel tests. Exploratory efficacy analyses included the homeostasis model of assessment beta-cell function (HOMA-B) and changes in lipid variables (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides).

Safety and tolerability variables were treatment-emergent AEs; clinical laboratory evaluations (haematology, serum chemistry and urinalysis); physical examinations; vital signs; oral temperature; ECG readings and the incidence of hypoglycaemia [blood glucose < 60 mg/dl (< 3.3 mmol/l) in presence of symptoms; blood glucose < 50 mg/dl (< 2.8 mmol/l) regardless of symptoms] and severe hypoglycaemia [defined as any episode requiring the assistance of another person to administer actively, carbohydrate, glucagons or other resuscitative actions, associated with blood glucose < 60 mg/dl (< 3.3 mmol/l)]. Because of the 2 : 2 : 1 randomisation scheme, data are presented using percentages first, followed by patient numbers within tables.

Results

Patients

The treatment groups were well balanced with respect to demographics and clinical characteristics (Table 1). The mean baseline HbA_{1c} across treatment groups ranged from 7.9% to 8.0% (57% of patients had a baseline HbA_{1c} < 8%), the mean baseline FPG across treatment groups ranged from 168 to 180 mg/dl (9.3–10.0 mmol/l), overall mean duration

Table 1 Demographic and other baseline characteristics for all randomised patients

Baseline characteristic	Metformin plus Placebo, *N* = 104	Alogliptin 12.5 mg, *N* = 213	Alogliptin 25 mg, *N* = 210
Gender			
Male	48% (50)	47.4% (101)	54.3% (114)
Female	52% (54)	52.6% (112)	45.7% (96)
Age (years)	56 ± 11	55 ± 11	54 ± 11
Age categories			
< 65 years	80% (83)	81% (173)	85% (179)
≥ 65 years	20% (21)	19% (40)	15% (31)
≥ 75 years	3% (3)	3% (7)	1% (2)
Race			
White	76% (79)	80% (170)	76% (159)
African American	7% (7)	2% (5)	6% (12)
Asian	6% (6)	8% (17)	9% (19)
Other race	11% (12)	10% (21)	9% (20)
Ethnicity			
Hispanic or Latino	24% (25)	31% (66)	32% (68)
Not Hispanic or Latino	76% (79)	69% (147)	68% (142)
Body mass index (kg/m^2)	32 ± 6	32 ± 5	32 ± 5
HbA_{1c} (%)	8.0 ± 0.9	7.9 ± 0.7	7.9 ± 0.8
< 8.0%	57% (59)	57% (122)	58% (121)
≥ 8.0%	43% (45)	43% (91)	42% (89)
Fasting plasma glucose (mmol/l)	10.0 ± 2.8	9.3 ± 2.4	9.5 ± 2.5
Diabetes duration (years)	6 ± 5	6 ± 5	6 ± 4
Systolic BP (mmHg)	129 ± 17	127 ± 13	127.3 ± 14.9
Diastolic BP (mmHg)	80 ± 9	78 ± 8	78 ± 8
Metformin dose (mg)	1868 ± 445	1837 ± 479	1846 ± 470
< 1500 mg/day at baseline	8.7 (9)	11.3 (24)	7.6 (16)
1500–2000 mg/day at baseline	71.2 (74)	67.1 (143)	72.4 (152)
> 2000 mg/day at baseline	20.2 (21)	21.6 (46)	20.0 (42)

Data are mean ± SD or % (*n*). BP, blood pressure.

of diabetes was 6 years and the overall mean baseline dose of metformin was 1847 mg. The patient population as a whole was predominantly white, comprising equal percentages of men and women and had a mean age of 55 years.

The overall disposition of patients enrolled and subsequently randomised to receive treatment is shown in Figure 1. Of the 596 patients enrolled, 527 continued to satisfy the eligibility criteria following the stabilisation period, were subsequently randomised to and receive treatment and were included in the efficacy and safety analyses. A total of 413 patients completed the study. The most commonly reported reasons for study discontinuation were voluntary withdrawal and AEs. A larger percentage of patients in the alogliptin 25 mg group prematurely discontinued the study (13.3%) for reasons other than hyperglycaemic rescue than did patients in the placebo (6.7%) or alogliptin 12.5 mg (8.0%) groups. This occurrence was primarily because of more subjects in the 25 mg alogliptin group than in other treatment groups voluntarily withdrawing from the study. However, evaluation of the subjects who withdrew because of voluntary withdrawal revealed that the reasons were typically associated with scheduling conflicts (e.g. work-related issues, family illness).

Glycaemic efficacy

In the presence of metformin, alogliptin at either dose produced significantly ($p < 0.001$) greater HbA_{1c} decreases from baseline to week 26 when compared with the changes exhibited by metformin alone (placebo). At week 26, the least squares (LS) mean (SE) changes in HbA_{1c} from baseline were −0.1 (0.1)%, −0.6 (0.1)% and −0.6 (0.1)%, respectively, among patients treated with placebo, alogliptin 12.5 mg and alogliptin 25 mg. Significant reductions in HbA_{1c} were evident as early as week 4 in both

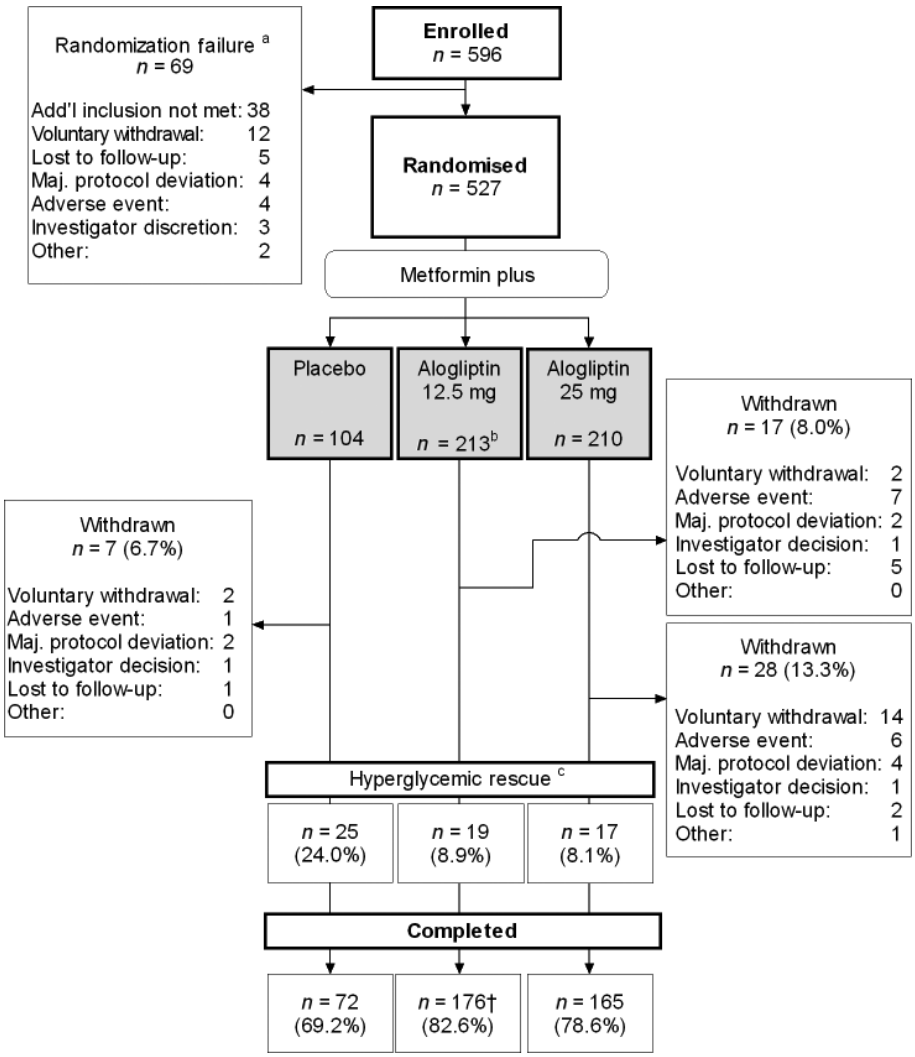

Figure 1 Disposition of patients. Shaded area represents the dataset used for safety and efficacy analyses; for inclusion in efficacy analysis, subject must have had both a baseline and one postbaseline value for the parameter being described. a – patients no longer meeting the eligibility criteria after the 4-week run-in/stabilisation period. b – for one patient in the 12.5 mg alogliptin group, the discontinuation page of the case report form was missing, accounting for the deficit in presented patient counts (patient was not counted as completed). c – hyperglycaemic rescue and withdrawn were mutually exclusive groups (i.e. those subjects rescued because of hyperglycaemia were not counted as discontinued). Reported as lack of efficacy

alogliptin groups ($p < 0.001$ vs. placebo) and persisted through week 26 (Figure 2A). Reductions in HbA_{1c} at week 26 were typically greater for patients with higher baseline HbA_{1c} levels, regardless of treatment group. Subgroup analyses demonstrated that regardless of age, gender, race, Hispanic ethnicity or baseline BMI, both doses of alogliptin resulted in meaningful reductions in HbA_{1c} relative to placebo.

Relative to patients in the placebo group, a significantly greater percentage of patients in both the alogliptin 12.5 and 25 mg groups achieved HbA_{1c} levels of $\leq 7.0\%$ ($p < 0.001$) and $\leq 6.5\%$ ($p < 0.05$) at week 26 (Table 2). Consistent with these findings, a significantly ($p < 0.001$) larger percentage of patients in both alogliptin groups had decreases from baseline in HbA_{1c} levels of $\geq 0.5\%$ and $\geq 1.0\%$ compared with patients receiving metformin alone (Table 2).

Treatment with alogliptin produced rapid, sustained and significant FPG reductions from baseline relative to placebo; these statistically significant ($p < 0.001$) reductions in FPG were evident as early as week 1 and persisted through the end of the study (Figure 2B). At week 26, the LS mean (SE) changes from baseline in FPG were 0 (4), −19 (3) and 17 (3) mg/dl [0.0 (0.2), −1.0 (0.1) and −1.0 (0.1) mmol/l] for the placebo, 12.5 mg alogliptin and 25 mg alogliptin groups respectively. Consistent with these findings, fewer patients in the alogliptin treatment

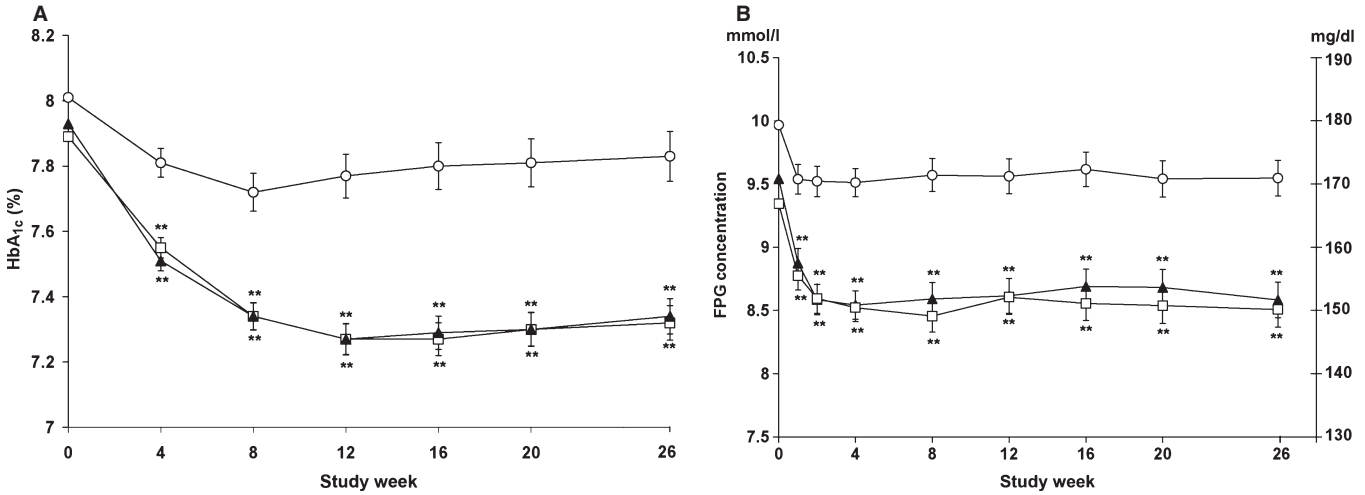

Figure 2 Measures of glycaemic control over time following once-daily administration of alogliptin 12.5 mg (open squares) and 25.0 mg (filled diamonds) vs. placebo (open circles) in combination with metformin. Baseline values are mean (SD); change from baseline values are LS mean values (SE). (A) HbA_{1c} [last observation carried forward (LOCF)]; baseline mean (SD) values were 8.0% (0.9%), 7.9% (0.7%) and 7.9% (0.8%) for placebo, alogliptin 12.5 mg and alogliptin 25 mg respectively. (B) Fasting plasma glucose; baseline mean (SD) values were 10.0 (2.8) mmol/l [180 (50) mg/dl], 9.3 (2.4) mmol/l [168 (44) mg/dl] and 9.5 (2.5) mmol/l [171.2 (46) mg/dl] for placebo, alogliptin 12.5 mg and alogliptin 25 mg respectively. **$p < 0.001$ vs. placebo

Table 2 Incidence of clinical response, marked hyperglycaemia and rescue for hyperglycaemia at week 26

	Metformin plus		
Incidence of clinical response	**Placebo, *N* = 104**	**Alogliptin 12.5 mg, *N* = 213**	**Alogliptin 25 mg, *N* = 207**
$HbA_{1c} \leq 7.0\%$	18% (19)	52% (110)	44% (92)
p-value (vs. placebo)		< 0.001	< 0.001
$HbA_{1c} \leq 6.5\%$	4% (4)	20% (42)	17% (36)
p-value (vs. placebo)		0.037	0.013
Decrease from baseline in $HbA_{1c} \geq 0.5\%$	27% (28)	58% (123)	59% (122)
p-value (vs. placebo)		< 0.001	< 0.001
Decrease from baseline in $HbA_{1c} \geq 1.0\%$	9% (9)	29% (61)	30% (62)
p-value (vs. placebo)		< 0.001	< 0.001
Decrease from baseline in $HbA_{1c} \geq 1.5\%$	6% (6)	9% (20)	12% (24)
p-value (vs. placebo)		0.334	0.065
Incidence of hyperglycaemic rescue and marked hyperglycaemia*			
Patients with marked hyperglycaemia	51% (53)	29% (61)	31% (65)
p-value (vs. placebo)		< 0.001	0.003
Patients rescued for hyperglycaemia	24% (25)	9% (19)	8% (17)
p-value (vs. placebo)		0.004	0.003

Data are % (*n*). *Marked hyperglycaemia was defined as FPG ≥ 11.1 mmol/l (200 mg/dl). FPG, fasting plasma glucose.

groups experienced marked hyperglycaemia [FPG ≥ 200 mg/dl (≥ 11.1 mmol/l)] compared with the placebo group at each time point and overall; the difference in overall incidence was statistically significant for both the 12.5 mg ($p < 0.001$) and 25 mg ($p = 0.003$) alogliptin groups compared with placebo using an extended Mantel-Haenszel test (Table 2). The incidence of hyperglycaemic rescue was significantly lower ($p \leq 0.004$) for patients in the alogliptin treatment groups compared with the placebo group (Table 2).

Endocrine pancreatic function, lipids and weight

There were no statistically significant differences between the alogliptin groups and placebo in the

changes from baseline to week 26 in fasting plasma proinsulin and insulin levels. Nevertheless, a trend towards lower proinsulin/insulin ratios in the presence of alogliptin was evident at each postbaseline time point, with both doses of alogliptin producing significantly ($p \leq 0.011$) greater reductions from baseline in proinsulin/insulin ratios compared with placebo from week 4 to week 16. Differences in HOMA-B between placebo and each alogliptin treatment group at week 26 were not statistically significant. There were no statistically significant differences among the treatment groups in the change from baseline to week 26 in fasting lipid variables.

Following 26 weeks of treatment, there were no statistically significant differences in change from baseline in weight between the placebo group and the alogliptin 12.5 and 25 mg treatment groups, suggesting that alogliptin is weight neutral. LS mean (95% CI) differences in weight relative to placebo were 0.0 (−0.7, 0.7) kg for alogliptin 12.5 mg and −0.3 (−0.9, 0.4) kg for alogliptin 25 mg.

Safety

The safety profile of alogliptin and metformin combination treatment, based on the results of this study, did not materially differ from that of metformin plus placebo. The administration of alogliptin 12.5 or 25 mg in combination with metformin for 26 weeks appeared to be generally well tolerated in this patient population. As shown in Table 3, the proportions of patients experiencing at least one AE was similar

Table 3 Summary of adverse events

	Metformin plus		
	Placebo, *N* = 104	**Alogliptin 12.5 mg, *N* = 213**	**Alogliptin 25 mg, *N* = 210**
Incidence of AEs	% (*n*)		
Patients with ≥ 1 AE	66% (69)	63% (134)	57% (118)
Patients with any study drug-related AE	10% (10)	11% (24)	13% (26)
Patients discontinued because of ≥ 1 AE	1% (1)	3% (7)	2% (4)
Patients with ≥ 1 SAE	4% (4)	3% (6)	4% (8)
Patients with ≥ 1 drug-related SAE	0	0	1% (2)
Number of treatment-emergent deaths	0	< 1% (1)	0
AEs occurring in ≥ 3% of any treatment group			
Gastrointestinal disorders	15% (16)	10% (22)	13% (26)
Diarrhoea	6% (6)	3% (6)	3% (7)
Infections and infestations	27% (28)	32% (68)	26% (53)
Urinary tract infection	4% (4)	7% (14)	3% (6)
Nasopharyngitis	6% (6)	6% (12)	3% (7)
Upper respiratory tract infection	7% (7)	5% (10)	2% (5)
Bronchitis	2% (2)	4% (9)	3% (6)
Sinusitis	5% (5)	2% (5)	2% (4)
Musculoskeletal and connective tissue disorders	17% (18)	15% (32)	11% (22)
Arthralgia	5% (5)	2% (4)	1% (3)
Pain in extremity	4% (4)	2% (5)	1% (3)
Nervous system disorders	6% (6)	9% (20)	8% (17)
Headache	2% (2)	4% (8)	2% (4)
Vascular disorders	7% (7)	3% (5)	3% (7)
Hypertension (worsening or newly diagnosed)	5% (5)	2% (4)	3% (6)
Overview of hypoglycaemic events			
Overall	3% (3)	1% (2)	0
Mild to moderate			
Symptomatic and blood glucose < 60 mg/dl	1% (1)	< 1% (1)	0
Symptomatic or asymptomatic and blood glucose < 50 mg/dl	0	< 1% (1)	0
Severe			
Any episode that requires assistance associated with a documented blood glucose < 60 mg/dl	0	0	0

AE, adverse event; SAE, serious adverse event.

across each treatment groups; a majority of AEs were of mild intensity and were considered unrelated to study drug by the investigator. The proportion of patients who experienced an AE that led to study discontinuation was low across treatment groups (1.9–3.3%). The most common AEs leading to discontinuation were abnormal liver enzymes (two patients in the alogliptin 12.5 mg group) and neuropathy [two patients (one in each alogliptin group)]. The abnormal liver enzymes were not considered by the investigator to be related to treatment, as both patients had elevated ALT levels at baseline. One of the subjects had a history of abnormal liver enzymes attributed by the investigator to fatty liver disease and one had a computed tomography scan after enrolment that revealed fatty liver. For both these patients, the ALT abnormalities were not associated with bilirubin elevations outside of the normal reference range.

The proportion of patients who experienced a serious AE (SAE) was similar across treatment groups (2.8–3.9%); discontinuations because of SAEs were noted for three patients in the alogliptin 12.5 mg group (prostate cancer, endometrial cancer and hypertensive heart disease) and two patients in the alogliptin 25 mg group (congestive heart failure and pulmonary embolism). Only the two SAEs in the alogliptin 25 mg group that lead to study discontinuation were considered by the investigator to be possibly related to study drug. One death was reported during the study (12.5 mg alogliptin). A 49-year-old woman with a history of hypertension died during an acute illness with gastrointestinal symptoms. A blood pressure (BP) of 153/76 mmHg was recorded approximately 1 month prior to death. The autopsy listed hypertensive heart disease as the cause of death; the investigator judged the event as unrelated to drug, noting that the structural changes in the heart were unlikely to have resulted from the study drug because of the relatively short exposure time (44 days) and the fact that no meaningful changes in BP were observed during the study.

Overall, the incidence of hypoglycaemia was low in all treatment groups; there were no severe hypoglycaemic events and no clinically significant hypoglycaemic episodes reported. The incidences of AEs occurring within the system organ classes of gastrointestinal disorders (10.3–15.4% across groups) were comparable across treatment groups. Skin-related AEs occurred in 7.7% of patients in the placebo group, 12.2% in the alogliptin 12.5 mg group and 11.6% in the alogliptin 25 mg group. Skin-related AEs that occurred only with alogliptin and in at least two alogliptin-treated patients, irrespective of alogliptin dose, were dry skin (1.2%, 5/420), pruritus (1.2%, 5/420), rash (2.1%, 9/420) and eczema (1.0%, 4/420). Only skin fissure (1.9%, 2/104) occurred only with placebo and in at least two placebo-treated patients. No skin-related AE was considered serious, although one patient (alogliptin 25 mg) discontinued because of a skin-related AE (drug eruption).

There were no clinically meaningful changes in laboratory test results (haematology, serum chemistry and urinalysis). Shifts from within normal limits at baseline to abnormal at subsequent study visits were infrequent and varied in direction with no apparent influence from alogliptin dosage. No clinically meaningful changes in vital signs (including systolic and diastolic BPs) were reported in this study.

Discussion

The results of this study demonstrate that in patients with type 2 diabetes inadequately controlled with metformin monotherapy once-daily treatment with alogliptin at doses of 12.5 or 25 mg produces statistically significant decreases in HbA_{1c} relative to placebo when administered on a background of metformin therapy. In the presence of alogliptin, statistically significant placebo-adjusted decreases in HbA_{1c} levels from baseline were evident as early as week 4 and persisted throughout the duration of the 26-week treatment period, with 52% of patients in the alogliptin 12.5 mg group and 44% of patients in the alogliptin 25 mg group, achieving the HbA_{1c} target of $\leq 7.0\%$ (compared with 18% of patients who achieved this target with metformin plus placebo). Approximately five (20%) and four (17%) times as many patients in the alogliptin 12.5 and 25 mg dose groups, respectively, achieved an $HbA_{1c} \leq 6.5\%$ compared with those patients who received metformin plus placebo (4%). This may point to the specific ability of DPP-4 inhibition in general and alogliptin treatment in particular to bring patients with relatively good glycaemic control to goal; this end result may be related to the lack of counterproductive effects (e.g. enhanced body weight, hypoglycaemic episodes), which are typical of alternative oral antidiabetic drugs, such as sulphonylureas, glinides and glitazones, that may be added to metformin according to the current guidelines (12,16).

Rapid, statistically significant improvements in FPG were also noted in the presence of alogliptin, as early as 1 week postdose and persisting throughout the study, a finding that has not been previously reported in the investigations of other DPP-4 inhibitors. The addition of alogliptin to metformin not only produced sustained HbA_{1c} and FPG improvements over metformin plus placebo, but also

achieved additive therapeutic effect without an increased risk of hypoglycaemia, gastrointestinal AEs or weight gain – unfavourable effects generally associated with current type 2 diabetes therapies (e.g. insulin, sulphonylureas, thiazolidinediones) (11,16,17). The safety profile of alogliptin was found to be favourable, with the overall frequency of AEs being lower among alogliptin-treated patients compared with placebo-treated patients and the number of hypoglycaemic events tending to be greater in the placebo group than in the alogliptin groups.

Metformin has been found to increase circulating total GLP-1 levels in both non-diabetic and type 2 diabetic patients (18), and it has been speculated that DPP-4 inhibition may interact with metformin to increase further the concentrations of intact, biologically active GLP-1 through the inhibition of GLP-1 degradation and inactivation. As reported by Migoya et al. (19), in a study of the DPP-4 inhibitor sitagliptin, when administered alone and in combination with metformin, active GLP-1 levels were increased by the combination of the two agents; however, total GLP-1 (i.e. active and inactive) was increased only by metformin monotherapy, pointing to the ability of metformin to augment nutrient-induced release of GLP-1 from L-cells. Conversely, active GIP concentrations remained unchanged with metformin monotherapy, but were increased following combination therapy with sitagliptin. This suggests that metformin's mechanism of action on active GLP-1 is unlike that of DPP-4 inhibitors, although the combination of the two drugs produces complimentary effects on intact, biologically active GLP-1. Taken together with the findings of our study, exploring the mechanism of GLP-1 release following administration of metformin, alogliptin and the combination of both agents may yield clinically relevant information. Furthermore, understanding how dietary patterns can augment the release of GLP-1 from L-cell may help optimise the therapeutic effectiveness of these drugs when used in combination therapy.

Overall, the results of this study are consistent with those noted in other clinical trials of DPP-4 inhibitors (20–23). No clear dose–response was observed for the efficacy end-points. This result is consistent with the near-complete inhibition (93–99%) of the DPP-4 enzyme 2–3 h after administration of a single dose alogliptin across a wide range of doses (25–200 mg) in healthy subjects (24) and > 84% inhibition at 24 h postdose after 14 days of once-daily dosing across the same dose range when administered to subjects with type 2 diabetes (25). This lack of dose–response has been observed in clinical trials with other DPP-4 inhibitors as well (15,26,27). Our results corroborate previous findings suggesting that DPP-4 inhibitor co-administration with metformin may currently be the only combination therapy that preserves two of the major advantages of metformin use: the absence of associated hypoglycaemia and weight gain.

As with other antidiabetic drugs in general (28) and other DPP-4 inhibitors in particular (29–32), the glucose-lowering effect as expressed by a change in HbA_{1c} or FPG is greater when baseline HbA_{1c} levels are higher. As a consequence, results from different trials can only be interpreted when taking into account the baseline HbA_{1c} concentrations or when comparing the dependency of HbA_{1c} reductions on baseline glycaemic control from different studies using different antidiabetic agents. In this study, for example, patients with a baseline $HbA_{1c} \geq 9\%$ experienced a drop in HbA_{1c} of $1.1 \pm 0.2\%$ after 26 weeks when treated with metformin plus alogliptin 25 mg/day. Without a direct comparison available, these results support the hypothesis that alogliptin is as effective a glucose-lowering agent in combination with metformin as has been reported for studies with sitagliptin and vildagliptin when added to metformin.

In conclusion, alogliptin provides a significant improvement in glycaemic control when added to metformin in patients not adequately controlled on metformin monotherapy, without an increased risk of AEs.

Author contributions

Michael Nauck contributed to the data analysis/interpretation, drafting and critical revision of the article and approval of the article. Graham Ellis, Penny Fleck, Craig Wilson and Qais Mekki all contributed to the data analysis/interpretation, critical revision of the content and approval of the article.

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