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Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy

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Aim: To evaluate the efficacy and safety of alogliptin, a potent and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor, in combination with glyburide in patients with type 2 diabetes inadequately controlled by sulphonylurea monotherapy.

Methods: After a 2-week screening period, adult patients 18–80 years of age entered a 4-week run-in/stabilization period in which they were switched from their own sulphonylurea medication to an equivalent dose of glyburide (open label) plus placebo (single blind). After the run-in period, patients were randomly assigned to double-blind treatment with alogliptin 12.5 mg ($n = 203$), alogliptin 25 mg ($n = 198$), or placebo ($n = 99$) for 26 weeks. The primary end-point was change from baseline to week 26 in glycosylated haemoglobin (HbA1c). Secondary end-points included clinical response rates and changes in fasting plasma glucose, β-cell function (fasting proinsulin, insulin, proinsulin/insulin ratio, and C-peptide, and homeostasis model assessment β-cell function), body weight, and safety end-points [adverse events (AEs), clinical laboratory tests, vital signs and electrocardiographic readings].

Results: The study population had a mean age of 57 years and a mean disease duration of 8 years; it was well balanced for gender (52% women) and was mainly white (71%). The mean baseline HbA1c was approximately 8.1% in each group. Significantly greater least squares (LS) mean reductions in HbA1c were seen at week 26 with alogliptin 12.5 mg (−0.38%) and 25 mg (−0.52%) vs. placebo (+0.01%; $p < 0.001$), and more patients in the alogliptin 25-mg group had HbA1c levels $\leq$7.0% at week 26 (34.8%, $p = 0.002$) vs. placebo (18.2%). Proportionately more patients in the alogliptin 12.5 mg (47.3%) and 25 mg (50.5%) groups had an HbA1c reduction $\geq$0.5% from baseline compared with patients in the placebo group (26.3%; $p < 0.001$). Minor improvements in individual markers of β-cell function were seen with alogliptin, but no significant treatment group differences were noted relative to placebo. Minor LS mean changes in body weight were noted across groups (placebo, −0.20 kg; alogliptin 12.5 mg, +0.60 kg; alogliptin 25 mg, +0.68 kg). AEs were reported for 63–64% of patients receiving alogliptin and 54% of patients receiving placebo. Few AEs were treatment limiting (2.0–2.5% across groups), and serious AEs (2.0–5.6%) were infrequent, similar across groups, and generally considered not related to treatment. The incidences of hypoglycaemia for placebo, alogliptin 12.5 mg and alogliptin 25 mg groups were 11.1, 15.8 and 9.6% respectively.

Conclusions: In patients with type 2 diabetes inadequately controlled by glyburide monotherapy, the addition of alogliptin resulted in clinically significant reductions in HbA1c without increased incidence of hypoglycaemia.

Keywords: alogliptin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1, sulphonylurea, type 2 diabetes mellitus
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Introduction

Although recent guidelines from the American Diabetes Association [1] and a consensus statement from the European Association for the Study of Diabetes [2] recommend metformin as the first-line drug for the treatment of type 2 diabetes, sulphonylureas remain widely prescribed as monotherapy. Despite the good initial efficacy of sulphonylureas and other oral agents, nearly half of the patients with diabetes in the USA do not achieve the American Diabetes Association treatment goal [glycosylated haemoglobin (HbA1c) <7.0%] [3], and fewer still achieve the more aggressive goal (HbA1c <6.5%) recommended by the European Association for the Study of Diabetes and other groups [4]. For most patients, achieving and maintaining treatment goals requires a combination of oral antidiabetic agents, with or without the use of insulin [5]. Thus, combination therapy has emerged as an important treatment approach, and additional options, particularly those that can be used safely in combination with other agents, are needed.

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones, released from the gut in response to intake of food, that stimulate insulin release from pancreatic β-cells when glucose levels are increased [6,7]. Additionally, GLP-1 inhibits glucagon secretion, slows gastric emptying and increases satiety [6,8]. The glucose-dependent insulin-releasing effects of GLP-1 and GIP are, however, short lived because of the rapid degradation of these peptides by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4). When DPP-4 is inhibited, GLP-1 and GIP remain in their intact, active form, and their effects on β-cells are extended [7]. The incretin effect in response to food intake is impaired in patients with type 2 diabetes [9]. However, this defect can be mitigated by augmenting the activity of GLP-1 through inhibition of the DPP-4 enzyme.

Alogliptin (alogliptin benzoate) is a potent and highly selective member of the DPP-4 inhibitor class of oral antidiabetic agents that is being developed as a once-daily treatment for patients with type 2 diabetes [10–12]. In a study conducted in patients with type 2 diabetes [13], once-daily administration of alogliptin for 14 days resulted in rapid and sustained inhibition of plasma DPP-4 activity and significant reductions in mean 4-h postprandial plasma glucose concentrations throughout the day. Pharmacokinetics and pharmacodynamics also supported a once-daily dosing schedule; after 14 days of dosing, plasma DPP-4 activity was inhibited by >80% at 24 h postdose and by >90% at peak effect at each evaluated dose (25, 100 and 400 mg) [13]. Alogliptin was generally well tolerated, and no dose-limiting toxicity was noted, even at the supratherapeutic doses of 100 and 400 mg [13].

Because DPP-4 inhibitors and sulphonylureas have different mechanisms of action, the combination of these agents may have additive effects for the treatment of type 2 diabetes [6,14]. Alogliptin also is unlikely to increase the risk of hypoglycaemia or result in clinically significant weight gain – effects that are associated with sulphonylurea treatment [6,14]. The present study was conducted to evaluate the efficacy and safety of alogliptin in combination with the sulphonylurea glyburide compared with glyburide plus placebo in patients with type 2 diabetes who had inadequate glycaemic control by sulphonylurea monotherapy.

Patients and Methods

Study Design

This 26-week, double-blind, randomized, placebo-controlled clinical study (identifier NCT00286468 at clinicaltrials.gov) was conducted at 124 centres in 16 countries from April 2006 to June 2007. The primary objective was to evaluate the change from baseline in HbA1c for patients treated with alogliptin and glyburide compared with patients treated with glyburide alone. Secondary objectives included evaluation of the safety of alogliptin and the effects of alogliptin on additional measures of glycaemic control, β-cell function, plasma lipids and weight. This study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice E6 and was approved by applicable institutional review boards. All patients provided written informed consent prior to participation.

Patients and Study Conduct

This study enrolled patients 18–80 years of age with a diagnosis of type 2 diabetes that was inadequately controlled (HbA1c values of 7.0–10.0%) with sulphonylurea monotherapy. Patients were required to have received a sulphonylurea for ≥3 months prior to screening but were excluded if they had received antidiabetic agents other than a sulphonylurea within the 3 months prior to screening. Patients also were excluded if they had a body mass index (BMI) <23 or >45 kg/m^2; a serum creatinine >2.0 mg/dl; a urine albumin/creatinine ratio >1000 μg/mg; prior laser treatment for proliferative diabetic retinopathy within 6 months; a history of treated diabetic gastroparesis; New York Heart Association classes III or

IV heart failure; a history of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within 6 months; received any investigational drug within 30 days; or previously participated in an investigational study of alogliptin. Use of weight loss drugs, bosentan or oral or systemically injected glucocorticoids was not allowed from 3 months prior to randomization until the end of treatment.

Study Treatments

Eligible patients were switched from their own sulphonylurea medication to open-label treatment with an equivalent dose of glyburide and single-blind placebo for a 4-week run-in/stabilization period. Patients were prescribed glyburide at a dosage of ≥10 mg/day (or ≥5 mg/day if documentation at screening indicated that the 10 mg/day dosage could not be tolerated). Patients received dietary and exercise advice according to local practices.

After completing the run-in period, patients with HbA1c values of 7.0–10.0%, fasting plasma glucose (FPG) <275 mg/dl, and ≥75% compliance with the single-blind placebo regimen (based on tablet count) were eligible to enter the double-blind treatment period if their sulphonylurea dose had been stable for the past 8 weeks. These patients were randomly assigned in a ratio of 2 : 2 : 1 to alogliptin 12.5 mg (daily dose), alogliptin 25 mg, or placebo in accordance with a permuted block schedule that was stratified for HbA1c at week −1 (HbA1c <8.0 vs. ≥8.0%) and for geographic region.

Study Assessments

Scheduled visits at baseline and throughout the 26-week double-blind treatment period required patients to fast ≥8 h and included the following: measurement of FPG; measurement of vital signs; clinical examination of skin and digits; review of diaries, adverse events (AEs) and glucometer readings; assessment of haematology and serum chemistry parameters; and dosing compliance. Plasma levels of HbA1c, proinsulin, insulin (measured as μIU/ml; 1 μIU/ml = 6 pmol/l), and C-peptide (measured as ng/ml; 1 ng/ml = 0.331 nmol/l) were assessed at baseline and at every visit from weeks 4 to 26.

Patients were trained in glucometer use, instructed on recognizing the signs and symptoms of hypoglycaemia and asked to maintain a diary of hypoglycaemic events. Hypoglycaemia was defined as blood glucose <60 mg/dl (to obtain blood glucose concentration in units of mmol/l, divide by 18) in the presence of symptoms or blood glucose <50 mg/dl with or without symptoms. The hypoglycaemic event was considered severe if it required the assistance of another person and, if the situation allowed measurement, blood glucose was found to be <60 mg/dl. If a patient experienced hypoglycaemia, the glyburide dose could be reduced once weekly in increments of 2.5 mg until hypoglycaemia was resolved. Rescue therapy for hyperglycaemia was initiated if FPG was ≥275 mg/dl after more than 1 week of treatment but prior to the week 4 visit, ≥250 mg/dl from the week 4 visit but prior to the week 8 visit, or ≥225 mg/dl from the week 8 visit but prior to the week 12 visit, or if HbA1c was ≥8.5% and was reduced by ≤0.5% from baseline at week 12 or later.

Statistical Analysis

The efficacy dataset included all patients who were randomized to double-blind treatment and received at least one dose of study drug; analysis of efficacy variables included data from patients with a baseline assessment and at least one post-baseline assessment. The safety dataset included all patients who received at least one dose of double-blind study drug. The study had 95% power to detect a mean difference of 0.4% in change from baseline in HbA1c between either alogliptin group and the placebo group with use of a two-sample *t*-test and assuming a standard deviation of 0.8%, a two-sided significance level of 0.05 and availability of evaluable data for ≥80% of randomized patients.

The primary efficacy end-point was change in HbA1c from baseline to week 26 with use of the last observation carried forward method. Secondary efficacy end-points included changes from baseline in FPG, proinsulin, insulin, proinsulin/insulin ratio, C-peptide and body weight, as well as incidence of marked hyperglycaemia (FPG ≥200 mg/dl) and of hyperglycaemia rescue. Responder analyses were used to determine percentages of patients with HbA1c reductions of ≥0.5 and ≥1.0% and of those who achieved HbA1c values ≤6.5 and ≤7.0%. Safety variables were treatment-emergent AEs, clinical laboratory test results, physical examination findings, vital signs, electrocardiographic readings and incidences of hypoglycaemia.

The treatment group difference in the primary end-point was assessed by analysis of covariance (ANCOVA) with geographic region, baseline HbA1c and baseline glyburide dose as covariates. To control for multiple testing associated with the primary analysis, treatment effect was first evaluated with the use of a contrast derived from the primary ANCOVA model at the two-sided 0.05 criterion significance level for the 25 mg dose compared with placebo. If this comparison was found to be significant, the significance of the treatment

effect for the 12.5 mg dose was evaluated analogously. For other continuous efficacy measures, change from baseline was analysed analogously to HbA1c, but with the corresponding baseline variable instead modelled as a covariate. Incidence variables in each treatment group were summarized with the use of descriptive statistics and were compared with nonparametric, covariance-adjusted, extended Mantel–Haenszel tests. ANCOVA models were used to examine changes in the homeostasis model assessment of β-cell function (HOMA-β) and changes in lipid variables. Descriptive statistics were used to analyse changes in HbA1c by sex, age, race, ethnicity and baseline BMI.

Results

Patient Disposition and Baseline Characteristics

Patient disposition is summarized in figure 1. Efficacy and safety analyses included all 500 patients who were randomly assigned to double-blind treatment (placebo, n = 99; alogliptin 12.5 mg, n = 203; alogliptin 25 mg, n = 198). Eighty-nine patients (17.8%) discontinued treatment because of the need for hyperglycaemic rescue, and 48 patients (9.6%) did not complete the study for other reasons, most commonly 'voluntary withdrawal' [placebo, n = 3 (3.0%); alogliptin 12.5 mg, n = 8 (3.9%); alogliptin 25 mg, n = 11 (5.6%)]. Voluntary withdrawals occurred most often for personal reasons rather than because of AEs or lack of efficacy.

Baseline demographic and clinical characteristics were similar across treatment groups (table 1). The study population had a mean age of approximately 57 years, a mean BMI of approximately 30 kg/m^2 and was predominantly white. The proportion of patients with a baseline HbA1c ≥8% (279/500; 55.8%) was greater than that of patients with a baseline HbA1c <8% (221/500; 44.2%). At study entry, the median daily glyburide dose was 10.0 mg. Nearly one-quarter of the study population was ≥65 years of age (table 1).

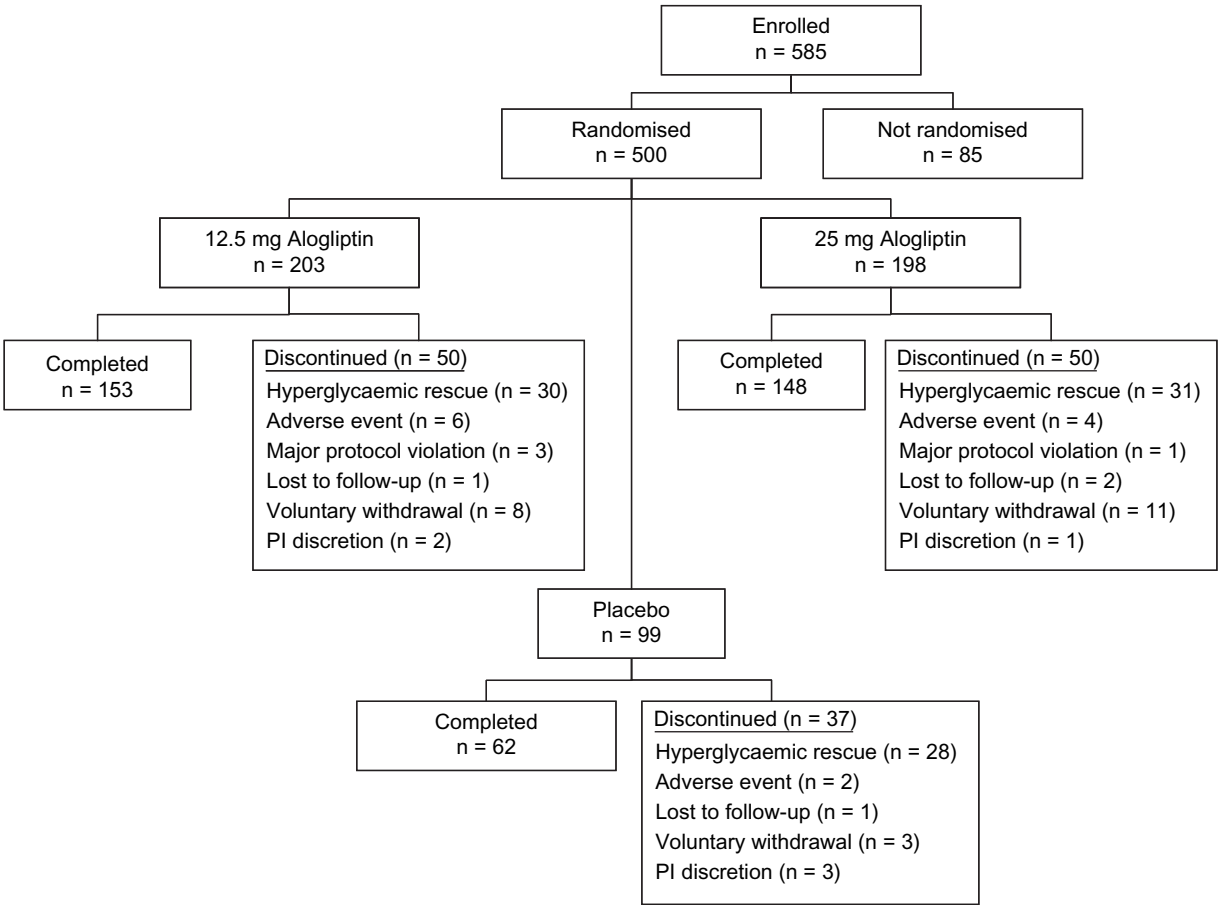

Fig. 1 Disposition of enrolled patients. PI, principal investigator.

Table 1 Baseline demographic and clinical characteristics

Characteristic	Glyburide		
	With placebo (n = 99)	With alogliptin 12.5 mg (n = 203)	With alogliptin 25 mg (n = 198)
Sex, n (%)			
Male	51 (51.5)	111 (54.7)	99 (50.0)
Female	48 (48.5)	92 (45.3)	99 (50.0)
Age (years)			
Mean (s.d.)	57.1 (10.0)	56.5 (11.1)	56.5 (11.7)
Median (range)	57.0 (32–80)	57.0 (26–80)	57.0 (21–80)
Age group, n (%)			
<65 years	72 (72.7)	153 (75.4)	145 (73.2)
≥65 years	27 (27.3)	50 (24.6)	53 (26.8)
≥75 years	4 (4.0)	8 (3.9)	6 (3.0)
Race, n (%)			
White	72 (72.7)	141 (69.5)	141 (71.2)
Asian	13 (13.1)	21 (10.3)	24 (12.1)
Black/African American	3 (3.0)	8 (3.9)	11 (5.6)
Native Hawaiian/Other Pacific Islander	0	0	0
American Indian/ Alaska Native	0	0	0
Other	11 (11.1)	33 (16.3)	22 (11.1)
Body mass index, kg/m^2			
Mean (s.d.)	30.0 (5.3)	30.2 (4.8)	30.0 (4.8)
Median	28.7	29.6	29.1
Range	23.0–44.2	22.3–44.5	23.0–45.1
Baseline HbA1c, n (%)			
Patients <8%	44 (44.4)	90 (44.3)	87 (43.9)
Patients ≥8%	55 (55.6)	113 (55.7)	111 (56.1)
Diabetes duration (years)			
Mean (s.d.)	7.7 (5.3)	7.8 (6.1)	7.6 (6.0)
Median	6.2	6.3	6.2
Range	0.4–25.9	0.6–41.3	0.4–30.3
Glyburide dose during the study (mg)			
Mean (s.d.)	11.2 (4.1)	12.3 (4.5)	12.4 (4.5)
Median	10.0	10.0	10.0
Range	5–20	5–30	3–30

HbA1c, glycosylated haemoglobin.

Glycosylated Haemoglobin

By week 26, least squares (LS) mean decreases in HbA1c were noted with both doses of alogliptin compared with a slight increase with placebo, resulting in statistically significant treatment group differences between each alogliptin dose and placebo (12.5 mg, −0.39%; 25 mg, −0.53%; placebo, +0.01%; $p < 0.001$ for each comparison) (figure 2). Analysis of the time course showed a significant treatment group difference in the LS mean change from baseline in HbA1c as early as week 4, which was sustained for the remainder of the study. The benefits of alogliptin on HbA1c reductions relative to placebo were realized irrespective of baseline HbA1c (figure 3) or glyburide dose. Moreover, clinically meaningful reductions in mean HbA1c were realized with alogliptin compared with placebo across subgroups of age, sex, race, ethnicity and baseline BMI (table 2).

Clinical Response Rate and Hyperglycaemia Rescue

Proportionately more patients in the alogliptin groups achieved HbA1c levels ≤7.0% at week 26 compared with patients in the placebo group; however, only the comparison between alogliptin 25 mg and placebo reached statistical significance (12.5 mg, 29.6%; 25 mg, 34.8%; placebo, 18.2%; $p = 0.057$ vs. 12.5 mg; $p = 0.002$ vs. 25 mg) (table 3). Proportionately more patients in the alogliptin groups compared with the placebo group achieved absolute reductions in HbA1c of ≥0.5 or ≥1.0% (table 3). Consistent with improvements in glycaemic control, significantly fewer hyperglycaemia rescues were necessary, proportionately, among patients treated with alogliptin compared with those treated with placebo [12.5 mg, 30/201 patients (14.9%); 25 mg, 31/198 patients (15.7%); placebo, 28/99 patients (28.3%); $p = 0.017$ vs. 12.5 mg; $p = 0.030$ vs. 25 mg].

Fasting Plasma Glucose

A minor increase in the LS mean change in FPG was observed with placebo {LS mean [standard error (SE)] change from baseline to week 26, +2.2 [4.8] mg/dl}, whereas mean decreases were noted with alogliptin 12.5 mg [−4.7 (3.3) mg/dl] and 25 mg [−8.4 (3.4) mg/dl]; however, differences between the active treatment groups and the placebo group in LS mean changes in FPG were not statistically significant ($p \geq 0.072$).

β-Cell Function

Modest improvements were observed in fasting insulin concentration, proinsulin : insulin ratio and HOMA-β with alogliptin treatment (table S1, *Supporting Information*). However, neither these changes nor changes in concentrations of proinsulin and C-peptide were significantly different with active treatment compared with placebo ($p \geq 0.124$).

Body Weight and Plasma Lipids

LS mean changes in body weight from baseline to week 26 were small and were not clinically meaningful. Nonetheless, significant treatment group differences in weight changes [LS mean (SE)] were observed between placebo (−0.20 [0.28] kg) and alogliptin 12.5 mg (+0.60 [0.19] kg;

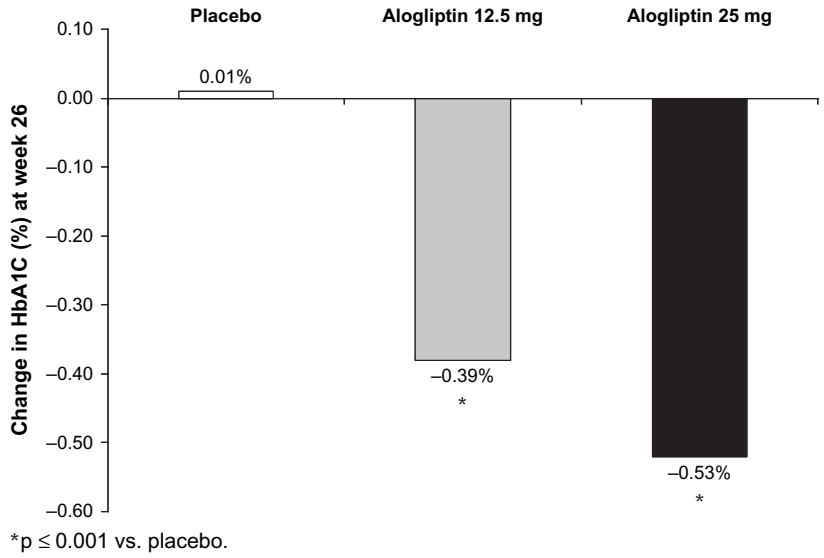

Fig. 2 Least squares mean change from baseline to week 26 in glycosylated haemoglobin (HbA1c). Least squares mean differences from placebo were −0.39 (95% confidence interval, −0.59 to −0.19) and −0.53 (95% confidence interval, −0.73 to −0.33 for the alogliptin 12.5- and 25-mg groups respectively).

p = 0.018) or 25 mg (+0.68 [0.19] kg; p = 0.010). Minor changes [LS mean (SE)] in lipid parameters were noted in each treatment group and, with the exception of an LS mean decrease in total cholesterol noted in the alogliptin 12.5 mg group [12.5 mg, −3.2 (2.0) mg/dl vs. placebo, +3.9 (2.9) mg/dl; p = 0.044], changes were similar with active treatment and placebo.

Safety

Alogliptin treatment generally was well tolerated at either dose, with 64 and 63% of patients in the alogliptin 12.5- and 25-mg groups, respectively, experiencing at least one AE during the 26-week treatment period compared with 54% of patients in the placebo group (table 4). The AE rate per 100 patient-years was calculated to account for

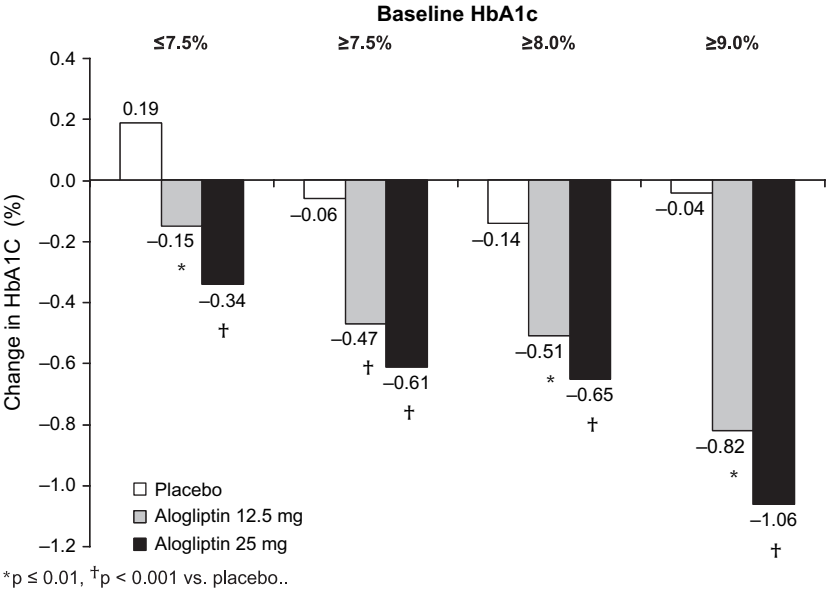

Fig. 3 Least squares mean change in glycosylated haemoglobin (HbA1c) at 26 weeks, analysed by baseline HbA1c value, for the placebo, alogliptin 12.5-mg and alogliptin 25-mg groups.

Table 2 Summary of mean change (s.d.) in HbA1c percentage from baseline to week 26 by patient subgroups

Subgroup	Glyburide		
	With placebo (n = 99)	With alogliptin 12.5 mg (n = 203)	With alogliptin 25 mg (n = 198)
Baseline HbA1c			
<8.0 (n = 243)	0.09 (0.76)	−0.24 (0.70)	−0.36 (0.69)
≥8.0 (n = 252)	−0.14 (1.01)	−0.51 (0.86)	−0.65 (1.02)
Age (years)			
<65 (n = 367)	−0.03 (0.97)	−0.29 (0.79)	−0.42 (0.90)
≥65 (n = 128)	−0.01 (0.70)	−0.64 (0.74)	−0.78 (0.81)
≥75 (n = 18)	0.20 (0.16)	−0.20 (0.73)	−0.95 (0.77)
Sex			
Male (n = 257)	0.01 (0.93)	−0.44 (0.74)	−0.64 (0.85)
Female (n = 238)	−0.05 (0.87)	−0.30 (0.85)	−0.38 (0.90)
Race			
Asian (n = 57)	0.35 (0.71)	−0.44 (0.96)	−0.25 (0.68)
Black (n = 22)	−0.03 (0.32)	−0.48 (0.61)	−0.70 (1.08)
White (n = 350)	−0.09 (0.89)	−0.36 (0.78)	−0.47 (0.90)
Other (n = 66)	−0.04 (1.17)	−0.36 (0.80)	−0.96 (0.75)
Ethnicity			
Hispanic or Latino (n = 248)	−0.24 (0.92)	−0.27 (0.80)	−0.60 (0.91)
Not Hispanic or Latino (n = 247)	0.19 (0.82)	−0.47 (0.78)	−0.42 (0.85)
Baseline body mass index			
<30 kg/m^2 (n = 274)	−0.02 (0.84)	−0.38 (0.79)	−0.68 (0.82)
≥30 kg/m^2 (n = 221)	−0.02 (0.98)	−0.37 (0.80)	−0.31 (0.92)

HbA1c, glycosylated haemoglobin.
Five patients had no post-baseline HbA1c assessment.

Table 3 Clinical response summary

Subgroup	Glyburide		
	With placebo (n = 99)	With alogliptin 12.5 mg (n = 203)	With alogliptin 25 mg (n = 198)
Baseline HbA1c (%)			
Mean (s.d.)	8.15 (0.85)	8.08 (0.83)	8.09 (0.90)
Median	7.90	7.90	8.00
Range	6.5–10.1	6.5–10.3	6.6–10.1
Patients achieving a given HbA1c, n (%)			
≤6.5%	7 (7.1)	19 (9.4)	28 (14.1)
p value*	–	0.762	0.174
≤7.0%	18 (18.2)	60 (29.6)	69 (34.8)
p value*	–	0.057	0.002
Patients achieving a given clinical response, n (%)			
HbA1c decrease ≥0.5%	26 (26.3)	96 (47.3)	100 (50.5)
p value*		<0.001	<0.001
HbA1c decrease ≥1.0%	13 (13.1)	38 (18.7)	59 (29.8)
p value*		0.149	<0.001

HbA1c, glycosylated haemoglobin.
*p values vs. placebo calculated with extended Mantel–Haenszel test without adjustments for multiple comparisons.

the disproportionately high incidence of withdrawal from the placebo group for hyperglycaemic rescue, which resulted in a treatment group difference in total exposure. With this calculated incidence rate, AEs occurred more frequently with 25 mg (426 per 100 patient-years) than with alogliptin 12.5 mg (417 per 100 patient-years) and least frequently with the placebo group (392 per 100 patient-years) (table 4). Most AEs in any treatment group were mild in intensity and not considered treatment related (table 4). Few patients experienced a treatment-limiting AE; discontinuation for this reason occurred in 2–3% of patients across treatment groups. AEs that occurred in ≥5% of patients in any treatment group were upper respiratory tract infection (more common with placebo), urinary tract infection, headache and hypertension (more common with alogliptin) (table 4).

Few serious AEs (SAEs) occurred during the study (24/500; 4.8%), and no dose-dependent trend in the incidence of SAEs between alogliptin groups was observed (table 4). Placebo was associated with the fewest reports of SAEs (2/99; 2.0%), with proportionately equal reports of SAEs with alogliptin 12.5 mg (11/203; 5.4%) and 25 mg (11/198; 5.6%) (table 4). The only SAE that occurred in more than a single patient in any treatment group was angina pectoris, which occurred in two patients in the alogliptin 25 mg group; this event was not treatment limiting in either case. One SAE of chronic cholecystitis was considered possibly related to the double-blind study drug (placebo), and one SAE of hypoglycaemia was considered probably related to the double-blind study drug (alogliptin 12.5 mg) and glyburide. Both these SAEs resolved with appropriate intervention. No deaths occurred during the study.

The incidence of hypoglycaemia was low and showed no relationship to double-blind treatment assignment. At least one hypoglycaemic episode was reported by 11.1% of patients who took placebo, 15.8% who took alogliptin 12.5 mg, and 9.6% who took alogliptin 25 mg (table 4). Severe hypoglycaemic episodes were reported by one patient (1.0%) in the placebo group, two patients (1.0%) in the alogliptin 12.5 mg group, and no patient in the alogliptin 25 mg group (table 4).

Relative to placebo, gastrointestinal AEs occurred with a similar incidence with alogliptin 12.5 mg and with a nominally higher incidence with alogliptin 25 mg; diarrhoea, however, occurred only in the alogliptin treatment groups (table 4). The incidence of skin-related AEs, which were specifically monitored during this study, was not increased when alogliptin was added to sulphonylurea treatment. The AE of skin lesion was reported only in the placebo group (2/99; 2.0%). Pruritus was the

Table 4 AE summary

Subgroup	Glyburide		
	With placebo (n = 99)	With alogliptin 12.5 mg (n = 203)	With alogliptin 25 mg (n = 198)
Patients with ≥1 AE, n (%)	53 (53.5)	129 (63.5)	125 (63.1)
No. of AEs per 100 patient-years	392.2	416.6	426.0
Patients with ≥1 treatment-related AE, n (%)	10 (10.1)	31 (15.3)	35 (17.7)
Patients with ≥1 serious AE, n (%)	2 (2.0)	11 (5.4)	11 (5.6)
Patients with ≥1 treatment-related serious AE, n (%)	1 (1.0)	1 (0.5)	0
Patients discontinuing treatment owing to AE, n (%)	2 (2.0)	5 (2.5)	4 (2.0)
Patients with AEs occurring in ≥5% of any group, n (%)			
Upper respiratory tract infection	6 (6.1)	4 (2.0)	5 (2.5)
Urinary tract infection	3 (3.0)	9 (4.4)	10 (5.1)
Headache	3 (3.0)	5 (2.5)	11 (5.6)
Hypertension	2 (2.0)	7 (3.4)	11 (5.6)
Patients with AEs of special interest, n (%)			
Hypoglycaemia	11 (11.1)	32 (15.8)	19 (9.6)
Symptomatic, blood glucose <60 mg/dl (mild to moderate)	8 (8.1)	18 (8.9)	16 (8.1)
Symptomatic or asymptomatic, blood glucose <50 mg/dl (mild to moderate)	6 (6.1)	10 (4.9)	8 (4.0)
Any episode that required assistance, associated with documented blood glucose <60 mg/dl (severe)	1 (1.0)	2 (1.0)	0
Gastrointestinal disorder*	14 (14.1)	26 (12.8)	36 (18.2)
Diarrhoea	0	8 (3.9)	9 (4.5)
Infection or infestation*	30 (30.3)	54 (26.6)	50 (25.3)
Bronchitis	3 (3.0)	3 (1.5)	1 (0.5)
Influenza	4 (4.0)	4 (2.0)	5 (2.5)
Nasopharyngitis	2 (2.0)	8 (3.9)	8 (4.0)
Skin or subcutaneous tissue disorder*	12 (12.1)	22 (10.8)	25 (12.6)
Pruritus	0	3 (1.5)	6 (3.0)

AE, adverse event.
*Other AEs in these system-organ classes were reported by <3% of patients in any treatment group or are listed in an earlier part of this table.

most commonly reported skin-related AE and was seen only in the alogliptin groups (table 4).

No clinically meaningful differences were noted among treatment groups with regard to changes in vital signs (including systolic and diastolic blood pressures), electrocardiographic parameters, or haematology, serum chemistry and urinalysis test results.

Discussion

In this study, the addition of alogliptin to ongoing glyburide therapy was associated with clinically significant reductions in HbA1c in patients with type 2 diabetes inadequately controlled by sulphonylurea monotherapy. Reductions in HbA1c were evident early after the commencement of treatment and were sustained throughout the 26-week treatment period. Proportionately more patients treated with alogliptin than with placebo achieved HbA1c levels ≤7.0%, irrespective of alogliptin dose. The benefit of glucose lowering observed with alogliptin was realized irrespective of age, sex, race, ethnicity and BMI; treatment with alogliptin resulted in the need for rescue medication significantly less frequently than did treatment with placebo. These benefits of alogliptin were achieved without a concurrent increase in the incidence of hypoglycaemia relative to placebo. Although most algorithms recommend metformin as first-line therapy for the treatment of type 2 diabetes, some patients cannot tolerate metformin and in some, metformin is contraindicated. Thus, a large number of patients are initially treated with sulphonylurea monotherapy. The results of the present study indicate that alogliptin may be a useful addition to improve glycaemic control in these patients who are not adequately controlled on sulphonylurea monotherapy.

Our results are consistent with those observed in similar studies of other DDP-4 inhibitors in combination with sulphonylureas [15,16]. This uniformity is true although the current study allowed enrollment of patients with HbA1c levels as low as 7.0%, whereas other studies excluded patients with baseline HbA1c levels <7.5% [16], and those with baseline HbA1c <7.5% who were taking monotherapy or no therapy [15]. This distinction is important because the efficacy of antidiabetic agents appears to be greater in patients with higher baseline HbA1c levels [17]. Consistent with this observation, alogliptin lowered HbA1c to a greater degree in patients with higher baseline HbA1c than in those with lower baseline HbA1c.

Mean changes in FPG by 26 weeks were small across all groups, with no statistically significant treatment group differences observed between either alogliptin dose and placebo. This observation is consistent with findings from a similar study with vildagliptin [15]. In contrast, significant treatment group differences were seen in a 24-week study in which patients received sitagliptin or placebo on a background of glimepiride or glimepiride plus metformin; this difference though appeared to be driven primarily by a marked increase in FPG with placebo (+18.4 mg/dl) rather than a clinically meaningful decrease with sitagliptin (−0.9 mg/dl) [16]. This difference in effects on FPG observed in the sitagliptin study could be attributed to the inclusion criteria; patients on dual or triple therapy with oral hypoglycaemic agents were eligible for study entry [16]. In

contrast, patients in the present study received only a sulphonylurea in the 3 months prior to screening.

Although no significant differences were observed between the alogliptin and placebo groups for any individual measure of β-cell activity, in the aggregate, the small improvements observed with alogliptin could suggest a tendency for benefit. The dominant effects of glyburide, which (similar to sulphonylureas) increases insulin secretion in a glucose-independent manner, could have obscured any β-cell parameter changes attributable to alogliptin. Studies of longer duration with more sophisticated dynamic measures of insulin secretion, such as responses to a standard meal, are needed to better characterize the effects of alogliptin on β-cell function [18].

Consistent with our results, previous studies have shown minor increases in mean weight when a DPP-4 inhibitor is added to a background of sulphonylurea therapy [15,16]. Sitagliptin 100 mg resulted in mean weight gain that was small but significantly greater [+0.8 kg; 95% confidence interval (CI), +0.4 to +1.2 kg] than that observed with placebo (−0.4 kg; 95% CI, −0.8 to +0.1 kg) [15]. Weight change with vildagliptin 50 mg (−0.1 kg) was similar to that with placebo (−0.4 kg; $p = 0.409$) [16]; vildagliptin 100 mg, however, resulted in a minor mean increase in weight that was significantly different (+1.3 kg; $p < 0.001$) relative to that seen with placebo [16].

AE reporting rates for alogliptin (63%) in this study were similar to those reported in similar studies with sitagliptin (56%) and vildagliptin (66–67%) [15,16], and no dose-dependent increase in the incidence of AEs was observed between the alogliptin 12.5 mg and 25 mg treatment groups. No individual AE was markedly more frequent for alogliptin treatment than for placebo. Addition of alogliptin to glyburide did not increase the risk of hypoglycaemia, despite improved glycaemic control. Our results differ from those for either vildagliptin or sitagliptin when administered with a sulphonylurea. After 24 weeks of treatment, hypoglycaemia was reported in 1.2 and 3.6% of patients administered vildagliptin 50 or 100 mg, respectively, in combination with glimepiride compared with 0.6% of patients given glimepiride alone [16]. Likewise, the addition of sitagliptin to glimepiride increased the incidence of hypoglycaemia from 1.8% with placebo to 12.2% with sitagliptin 100 mg [15].

In summary, alogliptin (12.5 or 25 mg) added to glyburide resulted in significant improvements in glycaemic control and was generally safe and well tolerated. These findings support the use of alogliptin in combination with a sulphonylurea agent in the management of type 2 diabetes.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Least squares mean change from baseline to week 26 in measures of β-cell function.

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Appendix

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Forty-three study investigators are not listed because no patients were enrolled at their sites; 1 investigator is listed only once, although he enrolled patients at two different sites.