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Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA_{1C} without causing weight gain or increased hypoglycaemia

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Aims: To assess the efficacy and safety of alogliptin added to insulin in patients with type 2 diabetes inadequately controlled with insulin alone or combined with metformin.
Methods: In this 26-week, double-blind, placebo-controlled study, 390 patients were randomized to receive alogliptin 12.5 mg (n = 131), alogliptin 25 mg (n = 129) or placebo (n = 130) once daily, as add-on to stable insulin therapy with or without metformin. The primary endpoint was change in haemoglobin A_{1C} (HbA_{1C}) at week 26.
Results: At week 26, mean HbA_{1C} changes from the mean baseline value of 9.3% were significantly greater for alogliptin 12.5 mg ($-0.63 \pm 0.08\%$) and alogliptin 25 mg ($-0.71 \pm 0.08\%$) than placebo ($-0.13 \pm 0.08\%$; $p < 0.001$). Significantly greater proportions of patients receiving alogliptin 12.5 or 25 mg than placebo had HbA_{1C} decreases of $\geqslant 0.5$, $\geqslant 1.0$ and $\geqslant 1.5\%$. Insulin doses remained unchanged, and there were no differences in the proportions of patients experiencing hypoglycaemia among placebo (24%), alogliptin 12.5 mg (27%) and alogliptin 25 mg (27%). Mean weight increases from baseline at week 26 were similar for placebo (0.6 ± 0.2 kg), alogliptin 12.5 mg (0.7 ± 0.2 kg) and alogliptin 25 mg (0.6 ± 0.2 kg). Incidences of overall adverse events, and of gastrointestinal, dermatological and infection-related events, were similar among groups.
Conclusions: Adding alogliptin to previous insulin therapy (with or without metformin) significantly improved glycaemic control in patients with type 2 diabetes inadequately controlled on insulin, without causing weight gain or increasing the incidence of hypoglycaemia. Further studies are warranted to explore the role of alogliptin added to optimized basal insulin regimens.
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Introduction

Over time, insulin becomes the mainstay of treatment for many patients with type 2 diabetes. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that 25 to 30% of individuals with diabetes use insulin, administered alone or with oral agents [1,2], yet few patients are able to achieve treatment goals. The NHANES 2003–2004 survey found that only 33% of patients receiving insulin alone, and 36% of those receiving insulin plus an oral agent, reached the haemoglobin A_{1C} (HbA_{1C}) target of less than 7% [1]. A review of a health maintenance organization database found that 26% of patients treated with insulin

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plus an oral agent, and 28% of those receiving insulin alone, achieved HbA_{1C} levels below 7% [3]. Safely reaching such glycaemic goals remains a substantial challenge because of the increased risk of hypoglycaemia and/or weight gain when adding agents that can enhance insulin action or complement the insulin regimen [4–6].

Alogliptin, a novel oral antidiabetic agent, is a potent and highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4) enzyme [7]. The DPP-4 enzyme rapidly inactivates glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, incretin hormones released postprandially from gut endocrine cells that stimulate glucose-mediated insulin secretion and inhibit postprandial glucagon secretion [8,9]. The present study was conducted to evaluate the efficacy, safety and tolerability of two doses of alogliptin (12.5 and 25 mg once daily [QD]) co-administered with insulin in patients with inadequately controlled type 2 diabetes.

Methods

Patients

This 26-week, double-blind, randomized, placebo-controlled trial enrolled patients 18–80 years of age with inadequately controlled type 2 diabetes on chronic insulin therapy. To enter the screening period, patients were required to have an HbA_{1C} level of $\geqslant$8.0% and a body mass index (BMI) of 23–45 kg/m^2, and to have received insulin, with or without concomitant metformin therapy, at a stable dose of $\geqslant$15 and $\leqslant$100 units per day (varying by $\leqslant$15% of the mean) for at least 8 weeks before randomization.

Patients were excluded from participation if they had a history of laser treatment for proliferative diabetic retinopathy, coronary angioplasty, coronary stent placement, coronary bypass surgery or myocardial infarction within the previous 6 months. New York Heart Association class III or IV heart failure, treated diabetic gastroparesis and cancer (other than squamous cell or basal cell carcinoma of the skin) that had not been in full remission for at least 5 years were also excluded.

Use of additional antidiabetic agents (other than metformin), weight loss drugs or glucocorticoids was not allowed from 3 months before randomization through the end of treatment.

Study Design

Patients eligible for screening entered a 4-week, single-blind, run-in/stabilization period, maintaining unchanged their existing insulin regimen (and metformin, if applicable). During this period, patients attended weekly visits to receive dietary and exercise counselling and instructions on maintaining records of blood glucose monitoring and learning to recognize and document hypoglycaemic events.

At completion of the run-in/stabilization period, eligible patients (HbA_{1C} level of $\geqslant$8.0%) were randomized to receive double-blind treatment with alogliptin 12.5 mg QD, alogliptin 25 mg QD or placebo for 26 weeks. Randomization was performed with an automated interactive voice response system using a randomization schedule generated before the start of the study. All patients continued their established daily insulin dose; in those receiving metformin the dose remained unchanged.

During the treatment period, patients returned to the study site at weeks 1, 2, 4, 8, 12, 16, 20 and 26 for fasting glucose and lipid measurements and review of glucose diaries and adverse event evaluations. Further safety assessments included clinical examination of skin and digits.

Patients were withdrawn from the study and completed an early termination visit if they fulfilled any of the following hyperglycaemic rescue criteria: fasting plasma glucose (FPG) $\geqslant$16.65 mmol/l after 1 week of treatment but before week 4; FPG $\geqslant$15.27 mmol/l from week 4 to week 8; FPG $\geqslant$13.88 mmol/l from week 8 to week 12 or $HbA_{1C} \geqslant$ 8.7% with a $\leqslant$0.5% decrease from baseline after week 12. Patients withdrawing for hyperglycaemic rescue were considered to have completed the study at that time. For all patients, a follow-up visit performed at week 28, or 2 weeks after discontinuation of study drug, included clinical examination, assessment of vital signs and review of adverse events (patients enrolling in an optional open-label extension study after completion may not have completed the 2-week follow-up visit).

The study was conducted using Good Clinical Practice according to the Declaration of Helsinki. The protocol was approved by the ethics committee at each investigational site, and all patients provided written informed consent.

Statistical Analyses

The planned sample size of 130 patients per treatment group was sufficient to detect a difference between alogliptin dose and placebo in HbA_{1C} change from baseline as small as 0.4% with 94% power using a two-sample *t*-test. This calculation assumes a standard deviation of 0.8%, a two-sided 0.05 significance level and no more than 20% of randomized patients withdrawing or having significant protocol deviations.

The primary efficacy variable was least squares (LS) mean change in HbA_{1C} from baseline to week 26. Secondary efficacy variables included LS mean changes from baseline to intermediate time points in HbA_{1C}; changes from baseline in FPG, body weight and lipid variables; and incidences of marked hyperglycaemia (FPG $\geqslant$11.1 mmol/l) and hyperglycaemic rescue. In addition, responder analyses summarized percentages of patients with HbA_{1C} changes from baseline of $\geqslant$0.5, $\geqslant$1.0, $\geqslant$1.5 and $\geqslant$2.0%.

The primary efficacy analysis used an analysis of covariance model to evaluate treatment effect through comparison of each active dose plus insulin with insulin alone. The model included study treatment, geographic region and baseline treatment regimen as class variables, and baseline daily insulin dose and baseline HbA_{1C} as continuous covariates. Starting with the 25 mg alogliptin dose, the treatment effect was evaluated with a stepdown procedure at the two-sided 0.05 significance level. If the result was statistically significant, the 12.5 mg dose was evaluated using the same model. Missing values were extrapolated using the last observation carried forward. Continuous secondary efficacy variables were analysed similarly to the primary analysis, with the corresponding variable's baseline value modelled as a covariate.

In analyses of clinical response, hyperglycaemia and hyperglycaemic rescue, incidences were compared between treatment groups using non-parametric, covariance-adjusted, extended Mantel–Haenszel tests.

The randomization scheme ensured that treatment assignments were balanced within the following stratification factors: HbA_{1C} at week −1 (<9.0 vs. $\geqslant$9.0%), geographic region and baseline treatment regimen (insulin alone vs. insulin plus metformin). Subgroup analyses of change from baseline in HbA_{1C} were conducted for subgroups defined by baseline HbA_{1C} value, metformin use, insulin dose, baseline BMI, sex, age, race and ethnicity.

Safety analyses included all patients who took at least one dose of double-blind study drug. Efficacy analyses were performed using the full analysis set (FAS), which for any efficacy variable included all patients who took at least one dose of double-blind study drug and had a baseline assessment and at least one post-baseline assessment of that variable.

Mild to moderate hypoglycaemia was defined as blood glucose <3.33 mmol/l with symptoms, or blood glucose <2.78 mmol/l with or without symptoms. Severe hypoglycaemia was defined as an episode requiring the assistance of another person to actively administer carbohydrate or glucagon, associated with a blood glucose <3.33 mmol/l, unless the clinical situation made obtaining a blood glucose measurement difficult. Patients received instructions on recognizing the signs and symptoms of hypoglycaemia during screening and through the week 2 visit.

Results

Disposition of Patients and Baseline Characteristics

In total, 477 patients were enrolled into the study at 110 sites in 13 countries, and 390 were randomized to receive double-blind study drug (130 receiving placebo, 131 alogliptin 12.5 mg and 129 alogliptin 25 mg). Of the 390 randomized patients, 389 patients took at least one dose of study drug and were included in the efficacy and safety analyses; 215 patients completed the study. Patient disposition and the reasons for withdrawing from the study are shown in figure 1.

Baseline demographic and clinical characteristics were similar among the three groups (table 1). Mean ages ranged from 55 to 56 years, the mean HbA_{1C} value was 9.3%, the mean BMI value was approximately 32 kg/m^2 and one third of patients identified themselves as being of Hispanic or Latino origin. Insulin types used were premixed insulins or insulin combinations (64% of patients), long-acting insulin (34%) and short-acting insulin (2%). Distributions of patients across these three types were similar among the treatment groups. Proportions of patients taking metformin in addition to insulin were 61, 59 and 56% in the placebo, alogliptin 12.5 mg and alogliptin 25 mg groups respectively.

Efficacy

At week 26, changes from baseline in mean HbA_{1C} were significantly greater for alogliptin 12.5 mg (−0.63%) and alogliptin 25 mg (−0.71%) than for placebo (−0.13%) ($p < 0.001$ for both doses vs. placebo). Significant decreases in HbA_{1C} levels were evident by week 4 in both alogliptin groups ($p < 0.001$ vs. placebo) and persisted through week 26 (figure 2A).

Significantly greater proportions of patients receiving alogliptin 12.5 or 25 mg had decreases in HbA_{1C} of $\geqslant$0.5, $\geqslant$1.0 or $\geqslant$1.5% than placebo (figure 2B). HbA_{1C} reductions at week 26 were also greater with both alogliptin doses than with placebo across various subgroups. In patients with a baseline HbA_{1C} below 8.5%, decreases were 0.1, 0.3 and 0.6% in the placebo, alogliptin 12.5 mg and alogliptin 25 mg groups respectively compared with decreases of 0.2, 0.7 and 0.7% in those with a baseline $HbA_{1C} \geqslant 8.5\%$. In patients taking metformin, decreases from baseline were 0.2, 0.7

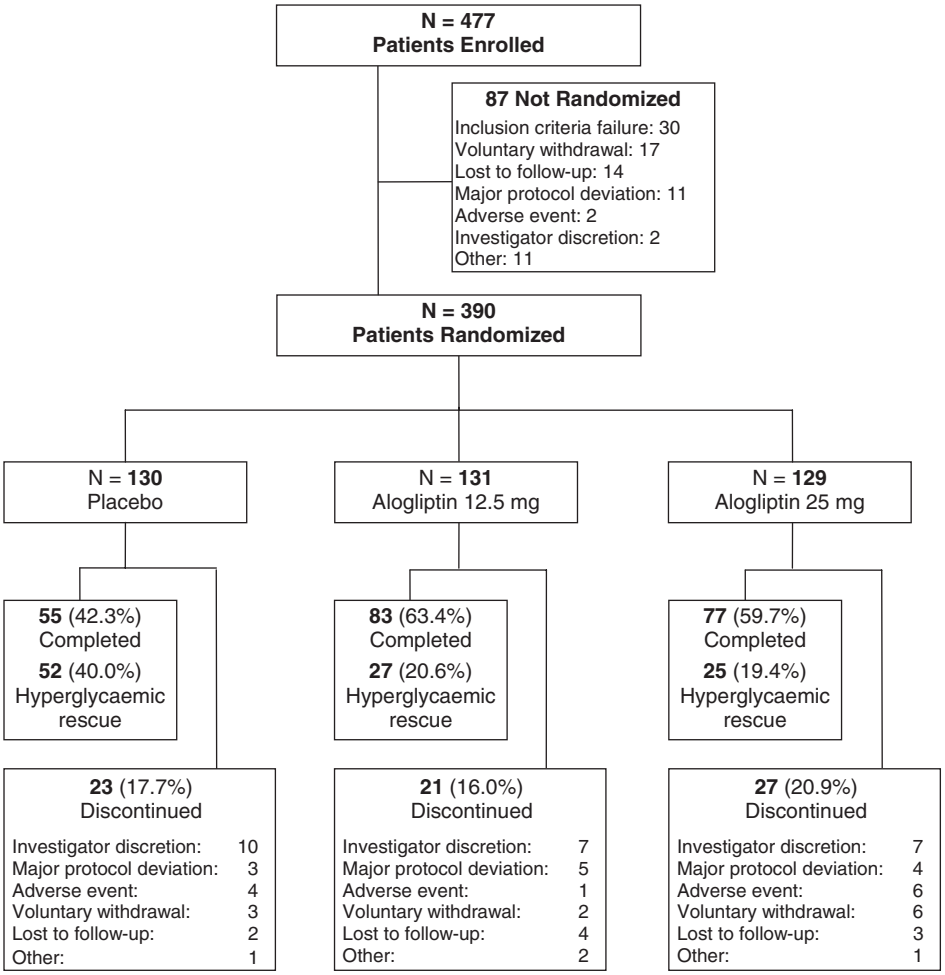

Fig. 1 Disposition of enrolled patients.

and 0.8% in the three treatment groups respectively compared with decreases of 0.1, 0.6 and 0.7% in those not taking metformin. HbA_{1C} decreased by 0.2, 0.6 and 0.8% respectively in those with insulin doses $\leqslant$60 units, and by 0.0, 0.7 and 0.5% in those with doses > 60 units. Regardless of gender, age (<65 or $\geqslant$65 years), ethnicity (Hispanic/Latino or not) or BMI (<30 or $\geqslant$30 kg/m^2), both doses of alogliptin showed meaningful decreases in HbA_{1C} compared with placebo.

A mean (±s.e.) FPG decrease from baseline of 0.6 ± 0.3 mmol/l was observed in the alogliptin 25 mg group at week 26 that was statistically significant compared with the increase of 0.3 ± 0.3 mmol/l observed with placebo ($p = 0.030$), but the change with alogliptin 12.5 mg (0.1 ± 0.3 mmol/l) was not different from placebo.

The overall incidences of hyperglycaemic rescue were significantly lower in the alogliptin 12.5 and 25 mg groups (21 and 20% respectively) than in the placebo group (40%; $p < 0.001$ for both comparisons). No substantial differences were observed among treatment groups in change from baseline in insulin dose, which, consistent with protocol requirements, were essentially unchanged at week 26 (increases of 0.6 ± 3.5 IU in the placebo group and 0.4 ± 5.7 IU in the alogliptin 12.5 mg group and a decrease of 0.2 ± 8.7 IU in the alogliptin 25 mg group).

Body weight at baseline and week 26 is shown in figure 2C. Mean changes from baseline were similar among the treatment groups: 0.6 ± 0.2, 0.7 ± 0.2 and 0.6 ± 0.2 kg in the placebo, alogliptin 12.5 mg and alogliptin 25 mg groups respectively.

Small mean decreases from baseline to week 26 occurred in both alogliptin groups in total cholesterol, HDL and LDL, and slight increases were observed in triglycerides, but none were statistically significant compared with placebo.

Table 1 Demographic and clinical characteristics at baseline: all randomized patients

Variable	Placebo (n = 130)	Alogliptin 12.5 mg (n = 131)	Alogliptin 25 mg (n = 129)
Age, years			
Mean ± s.d.	55.0 ± 10.6	55.4 ± 9.8	55.9 ± 10.2
Range	27–80	24–78	23–79
Category, No. (%)			
<65	109 (83.8)	112 (85.5)	106 (82.2)
⩾65	21 (16.2)	19 (14.5)	23 (17.8)
Sex, No. (%)			
Female	68 (52)	76 (58)	85 (66)
Male	62 (48)	55 (42)	44 (34)
Race, No. (%)			
White	89 (69)	81 (62)	85 (66)
Black/African-American	16 (12)	19 (15)	19 (15)
Asian	15 (12)	16 (12)	15 (12)
Other	10 (8)	15 (12)	10 (8)
Hispanic or Latino, No. (%)	42 (32)	45 (34)	42 (33)
Body mass index (mean ± s.d.)	32.4 ± 5.6	32.7 ± 5.5	32.3 ± 5.6
Weight, kg (mean ± s.d.)	91.0 ± 21.0	87.9 ± 19.9	86.7 ± 19.4
Diabetes duration, years (mean ± s.d.)	12.2 ± 7.1	12.1 ± 7.2	13.4 ± 6.3
Diabetes therapy, No. (%)			
Insulin only	51 (39)	54 (41)	57 (44)
Insulin plus metformin	79 (61)	77 (59)	72 (56)
Insulin dose, IU (mean ± s.d.)	57 ± 23	58 ± 23	55 ± 22
Metformin dose, mg (mean ± s.d.)*	1849.1 ± 642.7	1631.8 ± 645.6	1712.8 ± 573.6
HbA_{1C}, % (mean ± s.d.)	9.3 ± 1.1	9.3 ± 1.1	9.3 ± 1.1
FPG, mmol/l (mean ± s.d.)	10.9 ± 4.3	10.5 ± 3.4	10.3 ± 3.9

*Calculation includes only those receiving metformin.

Safety/Tolerability

The proportions of patients reporting any hypoglycaemic event were similar among the three groups: 24.0% for placebo, 26.7% for alogliptin 12.5 mg and 27.1% for alogliptin 25 mg (figure 2D). A total of six severe hypoglycaemic events occurred in two patients in the placebo group, and one severe event occurred in the alogliptin 25 mg group.

The proportions of patients experiencing an adverse event at any time during the study were slightly lower in the two alogliptin groups (67.9 and 66.7% respectively) than in the placebo group (73.6%) (table 2). Overall, the most common adverse events reported in the study were urinary tract infection, nasopharyngitis, headache, diarrhoea, arthralgia and peripheral oedema. The majority of adverse events were mild or moderate in intensity and were not considered treatment-related. The proportions of patients who discontinued because of adverse events were 3.1, 0.8 and 4.7% for placebo, alogliptin 12.5 mg and alogliptin 25 mg respectively. No single adverse event led to discontinuation in more than one subject.

Each study visit throughout the treatment period included a specific examination of the integrity of the skin and digits. Proportions of patients with skin-related adverse events, as well as adverse events relating to infections and to the gastrointestinal system, are displayed in table 2. The proportions of patients with skin-related or infection-related events were similar across treatment groups. Gastrointestinal events with a difference of two percentage points or more between alogliptin and placebo were abdominal pain (4.7% for alogliptin 25 mg vs. 0.8% for placebo), nausea (4.7% for alogliptin 25 mg vs. 2.3% for placebo), diarrhoea (5.4% for placebo vs. 0.8% for alogliptin 12.5 mg) and vomiting (3.1% for placebo vs. 0% for alogliptin 12.5 mg). Withdrawals because of adverse events in these systems were also similar between groups. Two patients withdrew because of gastrointestinal events (a placebo patient with haemorrhagic diverticulitis and an alogliptin 25 mg patient with acute pancreatitis), one patient because of an infection (an alogliptin 25 mg patient with body tinea) and two patients because of skin-related events (a placebo patient with eczema and an alogliptin 25 mg patient with urticaria).

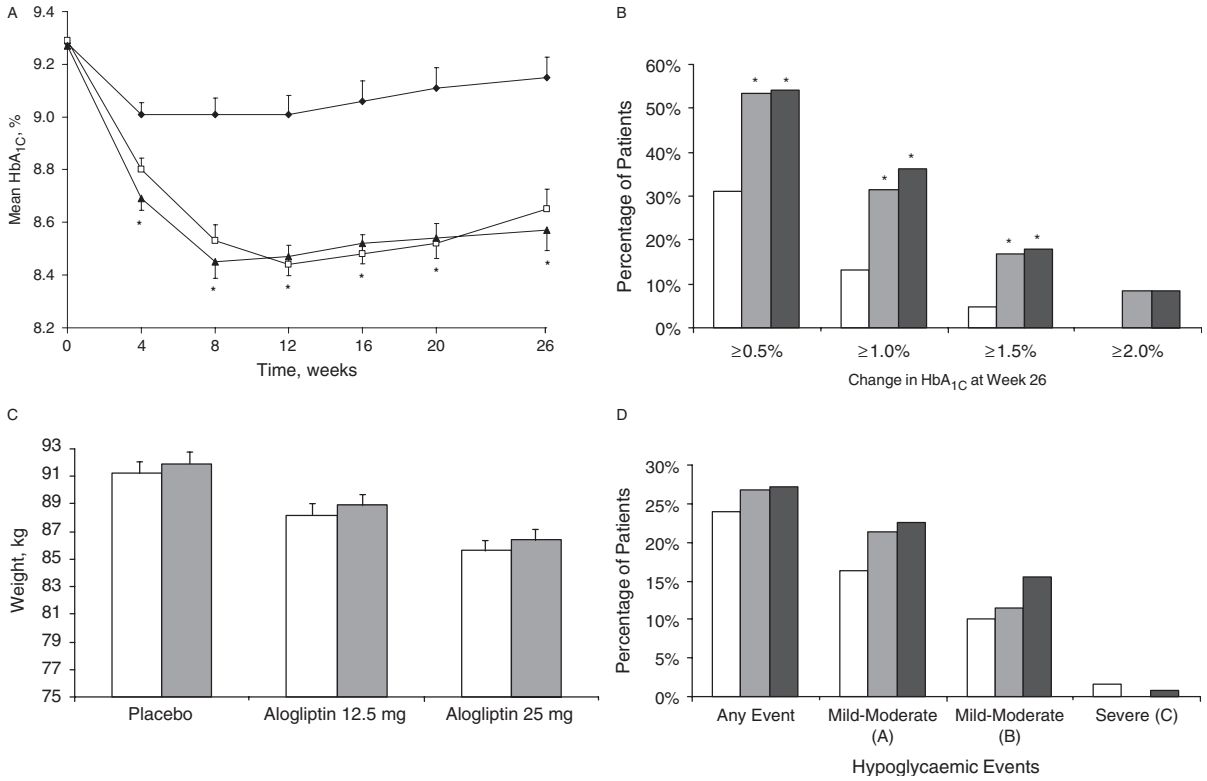

Fig. 2 A, Least-squares mean HbA_{1C} values (±s.e.) from baseline through week 26 for the placebo group (closed diamonds), the 12.5 mg alogliptin group (open squares) and the 25 mg alogliptin group (closed triangles). *$p < 0.001$ for both doses of alogliptin vs. placebo. B, Incidence of clinical response at week 26 based on change from baseline to week 26 in HbA_{1C} in patients receiving placebo (white bars), 12.5 mg alogliptin (grey bars) and 25 mg alogliptin (black bars). All patients showing the specified clinical responses are included, regardless of baseline HbA_{1C}. *$p \leqslant 0.05$ vs. placebo. C, Mean weight (±s.e.) at baseline (white bars) and week 26 (grey bars). Differences in least squares mean changes from baseline were not statistically significant between placebo and either alogliptin group. D, Incidence of hypoglycaemic events in patients receiving placebo (white bars), 12.5 mg alogliptin (grey bars) and 25 mg alogliptin (black bars). (A) Symptomatic with glucose <3.33 mmol/l; (B) symptomatic or asymptomatic with glucose <2.78 mmol/l; (C) required assistance, with glucose <3.33 mmol/l.

The proportions of patients who experienced a serious adverse event were similar across treatment groups (table 2). All of these events were considered by the investigator to be unrelated to study drug except that one patient in the alogliptin 12.5 mg group had serious adverse events of cholecystitis and pancreatitis considered by the investigator to be possibly related to study drug. The patient underwent cholecystectomy and the events resolved. A 72-year-old man in the alogliptin 12.5 mg group with numerous cardiac risk factors died of sudden cardiac arrest on day 71 of treatment. The death was considered not related to study drug.

Haematology, serum chemistry, vital signs, physical examinations and electrocardiographic (ECG) parameters showed no clinically meaningful differences between treatment groups.

Discussion

This study confirmed an independent effect of alogliptin by demonstrating consistent glucose-lowering effects of alogliptin in a population of significantly hyperglycaemic, obese, type 2 diabetic patients with non-optimized insulin therapy who maintained fixed insulin doses. Both doses of alogliptin were efficacious in this study, with HbA_{1C} reductions from baseline of 0.6 and 0.7% observed with alogliptin 12.5 mg and 25 mg respectively compared with 0.1% for placebo. The full effect of alogliptin treatment was observed by week 8 and was sustained throughout the 26-week treatment period. Categorical analyses of the proportions of patients with an HbA_{1C} decrease from baseline of 0.5, 1.0 and 1.5% also supported the efficacy of alogliptin when added

Table 2 Summary of adverse events: safety set

Variable	Placebo (n = 129)	Alogliptin 12.5 mg (n = 131)	Alogliptin 25 mg (n = 129)
Any adverse event	95 (73.6)	89 (67.9)	86 (66.7)
Any adverse event leading to withdrawal*	4 (3.1)	1 (0.8)	6 (4.7)
Any serious adverse event	6 (4.7)	8 (6.1)	7 (5.4)
Most common adverse events†			
Urinary tract infection	10 (7.8)	8 (6.1)	9 (7.0)
Diarrhoea	7 (5.4)	1 (0.8)	8 (6.2)
Nasopharyngitis	6 (4.7)	5 (3.8)	8 (6.2)
Peripheral oedema	4 (3.1)	4 (3.1)	7 (5.4)
Arthralgia	3 (2.3)	9 (6.9)	4 (3.1)
Headache	6 (4.7)	7 (5.3)	4 (3.1)
Any gastrointestinal event	22 (17.1)	19 (14.5)	27 (20.9)
Any infection/infestation event	40 (31.0)	43 (32.8)	38 (29.5)
Any skin-related event	14 (10.9)	15 (11.5)	14 (10.9)

All entries are No. (%) of patients. *Not including withdrawal owing to hyperglycaemic rescue. †Includes all events with incidence ⩾5% in any treatment group.

to insulin therapy. The effect of alogliptin 25 mg on FPG was small, but this result is not surprising considering the similar effects of other DPP-4 inhibitors on FPG; most of the HbA_{1C} effect is probably due to a reduction of postprandial hyperglycaemia, which was not measured in this study [10,11]. The fact that twice as many patients required hyperglycaemic rescue (40%) in the placebo group than in either alogliptin dose group (21 and 20% respectively) also attests to the glucose-lowering effect of alogliptin. The absence of a substantial dose response in the efficacy results between alogliptin 12.5 and 25 mg is consistent with observations in other efficacy studies [12,13], and with alogliptin's DPP-4 enzyme inhibition profile [14].

Fonseca *et al.* recently demonstrated that vildagliptin can improve glycaemic control when added to previous non-optimized insulin monotherapy, but the effect was slightly less than in the present study [15]. The smaller mean HbA_{1C} decrease from baseline (0.5%) in that study is probably due to the lower mean baseline HbA_{1C} value of 8.4%. In the present study, in the subgroup of patients with baseline HbA_{1C} of 8.5% or below, mean decreases of 0.3 and 0.6% were observed with alogliptin 12.5 mg and 25 mg respectively. It is noteworthy that vildagliptin showed greater HbA_{1C} decreases in elderly than in non-elderly patients (0.7 vs. 0.3%), but in the present study, alogliptin's efficacy was essentially indistinguishable between the two age groups.

Because the insulin doses in this study were not optimized, the course of the patients over the 26-week study period may not be considered representative of usual clinical practice. It is conceivable that with consistent insulin adjustments, as are usually carried out in clinical practice, alogliptin would have caused greater HbA_{1C} reductions, resulting in more patients reaching glycaemic targets. However, the fact that, by protocol design and for regulatory purposes, insulin dosages remained fairly unchanged throughout the study helped to clearly isolate and confirm the independent effect of alogliptin treatment.

Epidemiological analyses have demonstrated that lowering HbA_{1C} levels in patients with type 2 diabetes reduces the risk of long-term vascular complications [16]. Unfortunately, intensive glycaemic control, especially with insulin, sulfonylureas and thiazolidinediones, is associated with increased risk of hypoglycaemia and weight gain [6]. The present results, as well as those of other DPP-4 inhibitors [10,11], indicate that further glycaemic intervention may be possible without these treatment-limiting side effects. Weight changes from baseline to week 26 were small and almost identical between the groups, with increases of only 0.6, 0.7 and 0.6 kg for placebo, alogliptin 12.5 mg and alogliptin 25 mg respectively. Incidence of hypoglycaemia, which is a major barrier to insulin treatment, was low across the treatment groups in this study, and was not increased despite improvements in glycaemic control. Severe hypoglycaemia, although rare, was anecdotally observed more often in the placebo group.

In this study, the addition of alogliptin to an existing regimen of insulin alone or in combination with metformin was well tolerated. Almost 60% of the patients in this study were taking metformin, which is known to be associated with gastrointestinal symptoms, but alogliptin did not consistently affect gastrointestinal tolerability. The similarity between alogliptin and placebo in incidences of skin-related events is also noteworthy given that each study visit

included a direct clinical examination of skin and digits, increasing the potential for ascertainment bias, as investigators and patients were particularly vigilant regarding dermatologic effects.

The population in this study, with longstanding type 2 diabetes, significant obesity, marked hyperglycaemia and probably advanced β-cell failure, treated with non-optimized insulin regimens, represented a major challenge in attempting to demonstrate the benefits of alogliptin on glycaemic control by enhancing insulin secretion or reducing postprandial glucagon secretion. Nevertheless, the addition of alogliptin (at either 12.5 or 25 mg QD) to existing insulin therapy significantly improved glycaemic control, without increasing weight gain or the incidence of hypoglycaemia, and displayed a safety profile similar to that of insulin alone. Further studies are warranted in patients who start insulin therapy earlier using optimized basal insulin regimens, presumably with better islet cell reserve, in whom the addition of alogliptin to control postprandial hyperglycaemia may result in meaningful attainment of HbA_{1C} targets.

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