

**Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin in Patients With Type 2 Diabetes Mellitus and Inadequate Glycemic Control: A Randomized, Double-Blind, Placebo-Controlled Study**

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*Objective* — Evaluate the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin in drug-naïve patients with inadequately controlled type 2 diabetes.

*Research design and methods* — This double-blind, placebo-controlled, multicenter study included 329 poorly controlled patients randomized to once-daily treatment with alogliptin 12.5 mg (n=133), alogliptin 25 mg (n=131), or placebo (n=65) for 26 weeks. Primary efficacy end point was mean change from baseline in glycosylated hemoglobin (A1C) at final visit.

*Results* — At week 26, mean change in A1C was significantly greater ( $P < 0.001$ ) for alogliptin 12.5 mg (−0.56%) and 25 mg (−0.59%) than placebo (−0.02%). Reductions in fasting plasma glucose also were greater ( $P < 0.001$ ) in alogliptin-treated patients than in those receiving placebo. Overall incidences of adverse events (67.4%–70.3%) and hypoglycemia (1.5%–3.0%) were similar across treatment groups.

*Conclusions* — Alogliptin monotherapy was well tolerated and significantly improved glycemic control in patients with type 2 diabetes, without raising the incidence of hypoglycemia.

Clinical trial reg. no. NCT00286455, [clinicaltrials.gov](http://clinicaltrials.gov).

**ABBREVIATIONS:**

<b>AE</b>	adverse event
<b>ANCOVA</b>	analysis of covariance
<b>DPP-4</b>	dipeptidyl peptidase-4
<b>ECG</b>	electrocardiogram
<b>FPG</b>	fasting plasma glucose
<b>GLP-1</b>	glucagon-like peptide-1
<b>HOMA-B</b>	homeostatic model assessment of beta-cell function
<b>LOCF</b>	last observation carried forward
<b>SD</b>	standard deviation

Inhibition of dipeptidyl peptidase-4 (DPP-4) increases the concentration of glucagon-like peptide-1 (GLP-1), an incretin hormone that stimulates glucose-dependent insulin release, suppresses glucagon production, slows gastric emptying, reduces appetite, and may promote preservation of beta-cell function in patients with type 2 diabetes (1). Alogliptin is a novel, high-affinity, high-specificity DPP-4 inhibitor that produces rapid and sustained DPP-4 inhibition and significantly reduces postprandial plasma glucose concentrations in patients with type 2 diabetes (2,3). A phase 3 study was conducted to evaluate the efficacy and safety of alogliptin in adults with type 2 diabetes that was inadequately controlled with diet and exercise.

## **RESEARCH DESIGN AND METHODS**

Eligible patients were treatment-naïve (i.e., no current antidiabetes therapy and <7 days of therapy in the past 3 months) men and women, aged 18–80 years, with type 2 diabetes. Key inclusion criteria included A1C 7%–10%, BMI 23–45 kg/m<sup>2</sup>, treatment with diet and exercise for ≥1 month, and systolic/diastolic blood pressure ≤180/≤110 mm Hg. Patients received counseling on diet and exercise. Patients who completed a 4-week, single-blind run-in period with fasting plasma glucose (FPG) <275 mg/ml (15.27 mmol/l) and ≥75% compliance (by tablet count) were randomized (2:2:1) to 26 weeks of double-blind treatment with alogliptin 12.5 mg, alogliptin 25 mg, or placebo taken once daily before the first meal. Additional antidiabetic agents were prohibited.

Efficacy assessments included all randomized patients who received double-blind study drug. The primary end point was mean change from baseline in A1C at week 26. Other efficacy measures included changes in FPG, clinical response rates, incidences of marked hyperglycemia (FPG ≥200 mg/dl

[11.10 mmol/l]) and hyperglycemic rescue, and changes in body weight. Exploratory end points included changes in measures of pancreatic function (fasting insulin, fasting proinsulin, and homeostatic model assessment of beta-cell function [HOMA-B]) and lipid profiles. Treatment group differences for the primary end point were analyzed through analysis of covariance (ANCOVA), with treatment and geographic region as variables and baseline A1C and diabetes duration as covariates. The last observation carried forward (LOCF) method was used for imputing missing data; testing was 2-sided at a significance level of 0.05. Continuous secondary efficacy analyses were performed as for the primary analysis, except that the baseline covariate corresponds to the tested end point. Incidence variables were compared with nonparametric, extended Mantel-Haenszel tests; covariates were the same as for the primary end point.

The safety population included patients who took at least one dose of double-blind study drug. Safety assessments included adverse events (AEs), clinical laboratory findings, 12-lead electrocardiograms (ECGs), physical examination findings, vital signs, and hypoglycemic events. Skin and digits were specifically examined because of lesions previously observed in monkeys given DPP-4 inhibitors other than alogliptin (4–6). Safety findings were summarized with descriptive statistics.

## **RESULTS**

Of 420 patients enrolled (see online appendix which is available at <http://care.diabetesjournals.org>), 329 were randomized to double-blind treatment. Baseline characteristics were similar among treatment groups. Participants had a mean (standard deviation [SD]) age of 53.4 (11.1) years and a mean (SD) baseline A1C of 7.9%

(0.08) and were predominantly male (53.2%) and white (66.9%).

Mean A1C decreased significantly more with alogliptin 12.5 mg (−0.56%;  $P < 0.001$ ) or 25 mg (−0.59%;  $P < 0.001$ ) than with placebo (−0.02%) by week 26. Significant A1C reductions were observed as early as week 4 ( $P < 0.001$ ). FPG reductions were significantly greater with alogliptin than with placebo at week 26 ( $P < 0.001$ ) and as early as week 1 ( $P \leq 0.002$ ). The percentage of patients who required hyperglycemic rescue was significantly less with alogliptin (12.5 mg, 9.8%; 25 mg, 7.6%;  $P \leq 0.001$ ) than with placebo (29.7%). Minor reductions in weight with alogliptin were neither clinically nor statistically significant relative to placebo. Results for secondary efficacy measures and exploratory assessments are summarized in Table 1.

Overall incidences of AEs (67.4%–70.3%) and proportions of patients who discontinued because of AEs (1.5%–2.3%) were similar across treatment groups. Most AEs were mild or moderate in intensity. Serious AEs occurred without relation to dose (12.5 mg, 3.8%; 25 mg, 0.8%; placebo, 3.1%) and were considered unrelated to treatment. No patient died during the study. AEs from the most commonly observed categories occurred with similar or lower frequency in those given alogliptin versus placebo (infection, 28.0%–37.6%; gastrointestinal, 12.1%–14.3%). Headache occurred more frequently with alogliptin (6.8%–7.5%) than with placebo (4.7%). Despite increased surveillance for skin-related AEs, their overall incidence remained low (12.5%), albeit higher with alogliptin (12.8%–15.2%) than with placebo (6.3%), mostly because of pruritic events. Two patients discontinued because of skin-related AEs—one AE was considered possibly related to study drug (25 mg, moderate subcorneal pustular dermatosis); the other was judged unrelated to study drug (12.5 mg, moderate exacerbation of contact

dermatitis). No skin lesions resembling those noted in nonclinical studies of other DPP-4 inhibitors were observed. Hypoglycemia was rare (1.5%–3.0%), and no hypoglycemic event was considered an AE or was severe enough to require assistance. No clinically meaningful changes in laboratory test results, vital sign measurements, or ECG recordings were observed.

## **CONCLUSIONS**

Alogliptin monotherapy administered for 26 weeks to treatment-naïve patients with type 2 diabetes produced significant and clinically meaningful improvements in A1C. Glycemic improvements with alogliptin were rapid, sustained, and independent of age, race, and sex. Alogliptin treatment was well tolerated and was not associated with treatment-related serious AEs. A low incidence of hypoglycemia occurred with alogliptin and with placebo.

Weight gain is common among patients taking sulfonylureas and thiazolidinediones and may reduce treatment adherence (7, 8); thus the weight neutrality of alogliptin and other DPP-4 inhibitors may offer a therapeutic advantage (9–15). Increases in the proinsulin/insulin ratio with alogliptin versus placebo and a trend toward increased HOMA-B suggest that alogliptin, similarly to other DPP-4 inhibitors (9–11, 14, 15), may modestly improve pancreatic function.

In summary, the efficacy and safety of alogliptin monotherapy were comparable with those of other DPP-4 inhibitors (9–15). Alogliptin represents an effective treatment option whether given alone or in combination with antihyperglycemic agents from other classes.

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**Table 1—Results of secondary efficacy end points and exploratory assessments**

Parameter	Placebo (n=64)	Alogliptin 12.5 mg (n=133)	P value (vs placebo)	Alogliptin 25 mg (n=131)	P value (vs placebo)
A1C ≤6.5%, n (%)	7 (10.9)	23 (17.3)	0.818	27 (20.6)	0.294
A1C ≤7.0%, n (%)	15 (23.4)	63 (47.4)	0.001	58 (44.3)	0.008
A1C reduction ≥0.5%, n (%)	19 (29.7)	67 (50.4)	0.005	72 (55.0)	<0.001
A1C reduction ≥1.0%, n (%)	7 (10.9)	38 (28.6)	0.003	39 (29.8)	<0.001
FPG, LSM change (SE)	11.3 (5.24)	-10.3 (3.6)	<0.001	-16.4 (3.7)	<0.001
Hyperglycemic rescue, n (%)	19 (29.7)	13 (9.8)	0.001	10 (7.6)	<0.001
Marked hyperglycemia, n (%)	30 (46.9)	44 (33.1)	0.110	33 (25.4)	0.005
Body weight, LSM change (SE), kg	0.18 (0.37)	-0.09 (0.26)	0.539	-0.22 (0.26)	0.379
Proinsulin/insulin ratio, LSM change (SE)	0.046 (0.022)	-0.040 (0.015)	0.001	-0.038 (0.015)	0.002
HOMA-B, LSM change (SE)	-0.26 (5.98)	7.53 (3.99)	0.279	9.70 (4.08)	0.172
Total cholesterol, LSM change (SE), mg/dl	10.1 (3.3)	-1.2 (2.3)	0.006	-3.9 (2.3)	<0.001
HDL cholesterol, mg/dl, LSM change (SE), mg/dl	1.3 (0.9)	0.9 (0.6)	0.724	0.4 (0.6)	0.417
LDL cholesterol, LSM change (SE), mg/dl	4.6 (3.0)	-0.5 (2.1)	0.169	-0.4 (2.1)	0.178
Triglycerides, LSM change (SE), mg/dl	26.5 (14.8)	-5.8 (10.2)	0.074	-17.8 (10.4)	0.015

A1C, glycosylated hemoglobin A1C; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-B, homeostasis model of assessment–beta-cell function; LSM, least squares mean; SD, standard deviation; SE, standard error.