Initial Combination Therapy With Alogliptin and Pioglitazone in Drug-Naïve Patients With Type 2 Diabetes

**Objective** — To assess the efficacy and tolerability of alogliptin plus pioglitazone for initial combination therapy in drug-naïve type 2 diabetic patients.

**Research Design and Methods** — This 26-week, double-blind, parallel-group study randomized 655 patients with inadequately controlled type 2 diabetes to four arms: 25 mg alogliptin (A25) q.d. monotherapy, 30 mg pioglitazone (P30) q.d. monotherapy, or 25 mg alogliptin q.d. plus pioglitazone (P30) q.d. combination therapy. Primary efficacy was A1C change from baseline with the high-dose combination (A25 + P30) versus each monotherapy.

**Results** — Combination therapy with A25 + P30 resulted in greater reductions in A1C (−1.7 ± 0.1% from an 8.8% mean baseline) vs. A25 (−1.0 ± 0.1%, P < 0.001) or P30 (−1.2 ± 0.1%, P < 0.001) and in fasting plasma glucose (−2.8 ± 0.2 mmol/l) vs. A25 (−1.4 ± 0.2 mmol/l, P < 0.001) or P30 (−2.1 ± 0.2 mmol/l, P = 0.006). The A25 + P30 safety profile was consistent with those of its component monotherapies.

**Conclusions** — Alogliptin plus pioglitazone combination treatment appears to be an efficacious initial therapeutic option for type 2 diabetes.

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Because the pathogenesis of type 2 diabetes involves defects in both insulin secretion and insulin action, simplified, well-tolerated, and durably effective combination therapies are being considered as potential standard initial treatment strategies to increase the likelihood of achieving sustained glycemic targets (1–3). Two drug classes that have complementary modes of action and may prove efficacious in combination are thiazolidinediones (TZDs), which are insulin sensitizers that increase peripheral glucose uptake, and dipeptidyl peptidase (DPP)-4 inhibitors, which augment pancreatic insulin secretion and also reduce hepatic glucose output through a suppressive effect on pancreatic glucagon secretion (4,5). This phase 3 study was conducted in drug-naïve patients with type 2 diabetes inadequately controlled with diet and exercise to evaluate the effects of initial combination therapy with the DPP-4 inhibitor alogliptin and the TZD pioglitazone versus either component used alone.

**Research Design and Methods** — Eligible subjects were drug-naïve (no current antihyperglycemic medication or ≤6 days of any such agent within 3 months of screening) men and women (aged 18–80 years, with type 2 diabetes, A1C 7.5–11%, BMI 23–45 kg/m²) who had failed treatment with diet and exercise for ≥2 months prior to screening. Subjects were randomized to 26 weeks of once-daily treatment with 25 mg alogliptin (A25) monotherapy, 30 mg pioglitazone (P30) monotherapy, 12.5 mg alogliptin plus pioglitazone 30 mg (A12.5 + P30) combination therapy, or 25 mg alogliptin plus 30 mg pioglitazone (A25 + P30) combination therapy (see supplementary Fig. 1 in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-0159/DC1).

The primary efficacy end point was A1C change from baseline to week 26 or to study end in the intent-to-treat (ITT) population, with the last observation carried forward. Secondary glycemic control variables included A1C and fasting plasma glucose (FPG) changes from baseline at each study visit, percentage of patients achieving specific A1C goals, and frequency of glycemic rescue according to protocol when above the specific FPG or A1C values. Subgroup analyses by baseline A1C, sex, age-group, race, ethnicity, and baseline BMI were also performed.

Changes from baseline were analyzed using ANCOVA, with treatment and geographic region as class effects and baseline value as a continuous covariate. The primary analysis compared A25 + P30 with P30 and with A25, with a two-sided significance level of 0.05; if both comparissons were statistically significant, A12.5 + P30 was then compared with P30.

Adverse events (AEs) were recorded, and hypoglycemia was defined as blood glucose <3.3 mmol/l with symptoms suggesting low blood glucose or <2.8 mmol/l regardless of symptoms. Severe hypoglycemia was defined as any episode requiring assistance from another person.

**Results** — The study included 655 randomized patients, 654 of which comprised both the ITT and safety populations. Demographic and baseline characteristics were well balanced (51.1% female, 80.3% Caucasian, mean age 53
CONCLUSIONS — Initial combination therapy with the DPP-4 inhibitor alogliptin (25 mg) plus the TZD pioglitazone (30 mg) once daily for 26 weeks significantly improved glycemic control relative to monotherapy with either component in patients with type 2 diabetes inadequately controlled with lifestyle interventions. Despite a relatively high baseline A1C, this treatment strategy allowed nearly two-thirds of the patients to achieve A1C ≤7.0%. The safety profiles of alogliptin and pioglitazone administered together or separately were generally consistent with those previously reported for these two drug classes individually (6,7).

In summary, initial combination treatment with alogliptin and pioglitazone appears to be safe and was highly effective in short-term exposure and may be considered as an initial therapeutic option for type 2 diabetic patients not achieving adequate glycemic control with lifestyle changes alone or in those who cannot tolerate metformin therapy.
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