Effects of Vildagliptin on Glucose Control Over 24 Weeks in Patients With Type 2 Diabetes Inadequately Controlled With Metformin

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OBJECTIVE — We sought to evaluate the efficacy and safety of vildagliptin, a new dipeptidyl peptidase-4 inhibitor, added to metformin during 24 weeks of treatment in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a double-blind, randomized, multicenter, parallel group study of a 24-week treatment with 50 mg vildagliptin daily ($n = 177$), 100 mg vildagliptin daily ($n = 185$), or placebo ($n = 182$) in patients continuing a stable metformin dose regimen (≥1,500 mg/day) but achieving inadequate glycemic control (A1C 7.5–11%).

RESULTS — The between-treatment difference (vildagliptin − placebo) in adjusted mean change (AMΔ) ± SE in A1C from baseline to end point was −0.7 ± 0.1% ($P < 0.001$) and −1.1 ± 0.1% ($P < 0.001$) in patients receiving 50 or 100 mg vildagliptin daily, respectively. The between-treatment difference in the AMΔ fasting plasma glucose (FPG) was −0.8 ± 0.3 mmol/l ($P = 0.003$) and −1.7 ± 0.3 mmol/l ($P < 0.001$) in patients receiving 50 or 100 mg vildagliptin daily, respectively. Adverse events (AEs) were reported by 63.3, 65.0, and 63.5% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. Gastrointestinal AEs were reported by 9.6 ($P = 0.022$ vs. placebo), 14.8, and 18.2% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. One patient in each treatment group experienced one mild hypoglycemic event.

CONCLUSIONS — Vildagliptin is well tolerated and produces clinically meaningful, dose-related decreases in A1C and FPG as add-on therapy in patients with type 2 diabetes inadequately controlled by metformin.

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Abbreviations: AMΔ, adjusted mean change; AE, adverse event; AUC, area under the curve; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; ISR, insulin secretory rate; ITT, intent-to-treat; PPG, postprandial glucose; SAE, serious adverse event.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Vildagliptin is a new oral antidiabetes drug acting as a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for the rapid degradation of circulating glucagon-like peptide-1. Early studies suggest that vilgagliptin improves islet function in patients with type 2 diabetes by increasing both α- and β-cell responsiveness to glucose (1,2). In 12-week studies, vildagliptin given as monotherapy in drug-naïve patients with type 2 diabetes was shown to decrease fasting plasma glucose (FPG) and postprandial glucose (PPG) (3,4). Furthermore, a phase II study of vildagliptin added to metformin suggested that combining this DPP-4 inhibitor with metformin may be a particularly effective approach to improving glycemic control in patients with type 2 diabetes (5).

Metformin is the most commonly prescribed first-line antidiabetes drug worldwide, but due to the progressive worsening of blood glucose control during the natural history of type 2 diabetes, combination therapy usually becomes necessary (6). Therefore, it was of interest to ascertain the efficacy and tolerability of vildagliptin in combination with metformin in a larger phase III clinical trial. Accordingly, the present 24-week, multicenter, randomized, parallel-group, placebo-controlled study examined the effects of vildagliptin in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

RESEARCH DESIGN AND METHODS

— This was a 24-week, double-blind, randomized, placebo-controlled, parallel-group study conducted at 109 centers in the U.S. ($n = 79$), France ($n = 8$), Italy ($n = 6$), and Sweden ($n = 16$). Patients with type 2 diabetes inadequately controlled with metformin monotherapy attended one screening visit (visit 1, week −4), during which inclusion/exclusion criteria were assessed. Eligible patients were randomized at visit 2 (week 0) to receive 50 mg vildagliptin daily (as a q.d. dose), 100 mg vildagliptin

Table 1—*Patients studied and baseline characteristics of the primary ITT population*

	50 mg vildagliptin daily	100 mg vildagliptin daily	Placebo
Analysis populations			
Randomized	177	185	182
Safety	177	183	181
Primary ITT	143	143	130
ITT	174	175	171
Meal test participants	55	58	54
Primary ITT population			
Age (years)	54.3 ± 9.7	53.9 ± 9.5	54.5 ± 10.3
Sex			
Male	82 (57.3)	88 (61.5)	69 (53.1)
Female	61 (42.7)	55 (38.5)	61 (46.9)
Race			
Caucasian	106 (74.1)	106 (74.1)	95 (73.1)
Hispanic or Latino	24 (16.8)	19 (13.3)	24 (18.5)
Black	9 (6.3)	13 (9.1)	9 (6.9)
All other	4 (2.8)	5 (3.5)	2 (1.5)
BMI (kg/m^2)	32.1 ± 5.3	32.9 ± 5.0	33.2 ± 6.1
A1C (%)	8.4 ± 0.9	8.4 ± 1.0	8.3 ± 0.9
FPG (mmol/l)	9.7 ± 2.2	9.9 ± 2.6	10.1 ± 2.4
Disease duration (years)	6.8 ± 5.5	5.8 ± 4.7	6.2 ± 5.3
Duration of metformin (months)	17.8 ± 23.2	17.9 ± 23.0	15.9 ± 16.7
Metformin dose (mg/day)	2,126 ± 298	2,099 ± 328	2,102 ± 320

Data are *n*, mean ± SD, or *n* (%).

daily (as equally divided doses), or placebo. Efficacy and tolerability were assessed during four additional visits, at weeks 4, 12, 16, and 24 of treatment.

The study enrolled patients with type 2 diabetes who had been treated with metformin monotherapy for at least 3 months and who had been on a stable dose of ≥1,500 mg daily for a minimum of 4 weeks before visit 1. Participants were required to have A1C in the range of 7.5–11.0% at the screening visit, and, if they were not at that time receiving their maximum-tolerated dose, they agreed to increase their metformin dose to 2,000 mg daily at visit 1. Male and female patients (nonfertile or of childbearing potential using a medically approved birth control method) aged 18–78 years, inclusive, with a BMI in the range of 22–45 kg/m^2, inclusive, and with FPG <15 mmol/l were eligible to participate.

Patients were excluded if they had a history of type 1 or secondary forms of diabetes, acute metabolic diabetes complications within the past 6 months, congestive heart failure requiring pharmacologic treatment, myocardial infarction, unstable angina, or coronary artery bypass surgery within the previous 6 months. Liver disease such as cirrhosis or chronic active hepatitis also precluded participation, as did renal disease or renal dysfunction as suggested by elevated serum creatinine levels ≥132 μmol/l for male and ≥123 μmol/l for female subjects.

Study assessments

A1C, FPG, body weight, and vital signs were measured at each study visit. Standard hematology and biochemistry laboratory assessments were made at each visit except week 16. Fasting lipid levels (triglyceride and total, LDL, HDL, non-HDL, and VLDL cholesterol) were measured, and electrocardiograms were performed at screening and at weeks 0, 12, and 24. Standard breakfast meal tests (500 kcal; 60% carbohydrate, 30% fat, and 10% protein) were performed at weeks 0 and 24 in patients agreeing to participate (~30% of patients in each treatment group) for assessment of β-cell function and prandial glucose control. Insulin secretory rate (ISR) was calculated by deconvolution of plasma C-peptide levels (7). The 2-h area under the curves (AUCs) for ISR and glucose were calculated with the trapezoidal method, and the ratio of ISR AUC to glucose AUC was used as a measure of β-cell function.

All adverse events (AEs) were recorded. Patients were provided with glucose monitoring devices and supplies and instructed on their use. Hypoglycemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement <3.1 mmol/l plasma glucose equivalent. Severe hypoglycemia was defined as any episode requiring the assistance of another party.

All laboratory assessments were made by central laboratories. All assessments except A1C were performed by Bio Analytical Research Corporation (BARC). Assays were performed with standardized and validated procedures according to good laboratory practice. A1C measurements were performed by either BARC-EU (Ghent, Belgium) for European subjects or by the National Glycohemoglobin Standardization Program network laboratory, Diabetes Diagnostics Laboratory (Columbia, MO), or Covance-US (Indianapolis, IN) for U.S. subjects. All samples from any single patient were measured by the same laboratory.

Data analysis

The primary efficacy variable was the change in A1C from baseline at study end point using last observation carried forward for patients who discontinued early. Secondary efficacy parameters included FPG, fasting plasma lipids, and body weight. The primary efficacy analyses were performed with data from patients who had a reliable screening A1C value ≥7.4%, received at least one dose of study medication, and had a reliable baseline and at least one reliable postbaseline A1C measurement. This population is referred to as the primary intent-to-treat (ITT) population and was prespecified as the main efficacy population. Changes from baseline in primary and secondary end points were analyzed using an ANCOVA model with treatment and pooled center as the classification variables and baseline value as the covariate. Analyses were carried out using two-tailed tests and a statistical significance level of 0.05. Multiple testing was adjusted for using Hochberg's multiple testing step-up procedure to maintain an overall two-sided significance level of 0.05 (8). The data reported for safety and tolerability included all patients who were exposed to at least one dose of study drug and had at least one postbaseline safety assessment.

All participants provided written informed consent. The protocol was approved by the independent ethics

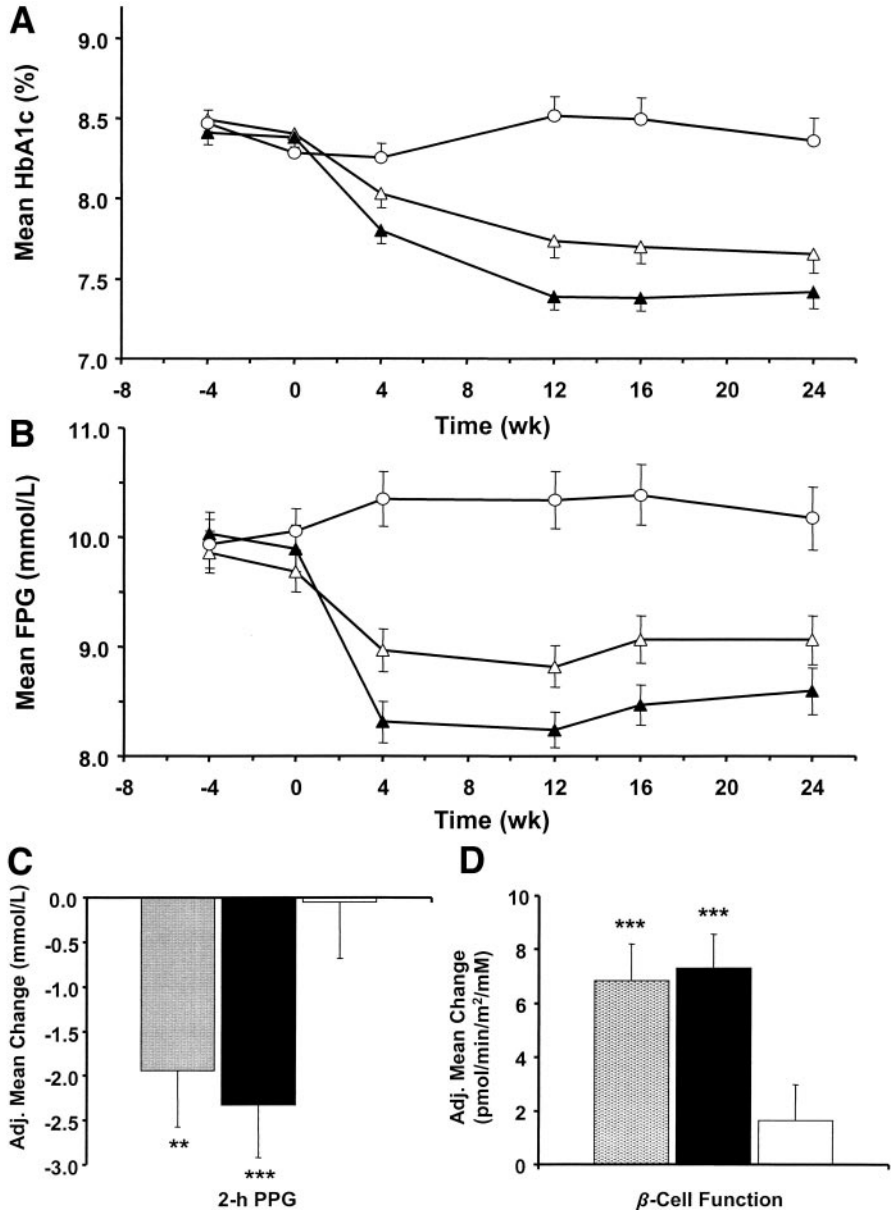

Figure 1—A *and* B*: Mean ± SE A1C (*A*) and FPG* (B) *during 24 weeks of treatment with 50 mg vildagliptin daily (△), 100 mg vildagliptin daily (▲), or placebo (○) in patients with type 2 diabetes continuing stable metformin dose regimen (≥1,500 mg/day).* C *and* D*: Adjusted mean change (±SE) in 2-h postprandial glucose (2-h PPG)* (C) *and β-cell function* (D) *and after 24-week treatment with 50 mg vildagliptin daily (▨), 100 mg vildagliptin daily (■), or placebo (□) in patients with type 2 diabetes continuing stable metformin dose regimen (≥1,500 mg/day).* ***P < 0.001; **P = 0.001 vs. placebo.*

committee/institutional review board at each study site, and the study was conducted using good clinical practice in accordance with the Declaration of Helsinki.

RESULTS — Patient disposition from screening through study end point is summarized in supplemental Fig. 1 (available in an online appendix at http://dx.doi.org/10.2337/dc06-1732), and baseline demographic and metabolic characteristics of the primary ITT population are reported in Table 1. A total of 544 patients were randomized; 416 patients comprised the primary ITT population, and >83% of patients in each treatment group completed the study. In the primary ITT population, the groups were well balanced at baseline, with A1C averaging 8.4% and FPG averaging 9.9 mmol/l in the combined cohort. Participants were predominantly Caucasian and obese, with a mean age of 54 years and mean disease duration of 6.2 years. Patients had been using metformin at a stable dose for an average of 17 months; the mean metformin dose was ~2,100 mg/day. Standard breakfast meal test was performed at weeks 0 and 24 in a subgroup of 163 patients with characteristics representative of the whole ITT population, of whom 53 were treated with 50 mg vildagliptin daily, 56 with 100 mg daily, and 54 were in the placebo group.

Efficacy

All reported efficacy data derive from the primary ITT population. Similar findings were obtained in the ITT population for all the variables measured (data not shown). The time courses of mean A1C and FPG during the 24-week treatment with 50 mg vildagliptin daily, 100 mg daily, or placebo added to metformin are depicted in Fig. 1*A* and *B*, respectively. The mean baseline A1C was 8.4 ± 0.1% in both groups of patients randomized to vildagliptin and 8.3 ± 0.1% in patients randomized to placebo. The adjusted mean change (AMΔ) A1C was 0.2 ± 0.1% in patients receiving placebo and −0.5 ± 0.1 and −0.9 ± 0.1% in patients receiving 50 mg and 100 mg vildagliptin daily, respectively. The between-treatment difference (vildagliptin − placebo) was −0.7 ± 0.1% with 50 mg vildagliptin daily ($P < 0.001$) and −1.1 ± 0.1% with 100 mg vildagliptin daily ($P < 0.001$).

To allow better appreciation of the response to treatment, supplemental Fig. 2 depicts the number of patients in each treatment group who experienced a deterioration of glycemic control (ΔA1C >0.3%), no meaningful change (ΔA1C −0.3 to 0.3%), a moderate improvement (ΔA1C −0.4 to −1.0%), or a marked improvement (ΔA1C −1.1 to −2.0% or ΔA1C <−2.0%). In the group receiving placebo and continuing metformin treatment, glycemic control deteriorated in 35.4% of patients and did not change meaningfully in 30.8% of patients. In the placebo group, some improvement was experienced by approximately one-third of patients. In contrast, in the group receiving 50 mg vildagliptin daily, more than two-thirds of patients experienced meaningful (37.8%) or marked (29.4%) improvement in glycemic control. In the group receiving 100 mg vildagliptin daily and continuing metformin treatment, more than three-quarters of patients experienced a meaningful (41.3%) or marked (37.1%) improvement in glycemic control.

Responder rates (percentage of patients achieving end point A1C <7.0%) were also calculated and stratified according to baseline A1C levels. In patients with baseline A1C ≤7.9%, 26 of 52 patients receiving 50 mg vildagliptin daily (50.0%), 31 of 57 patients receiving 100 mg vildagliptin daily (54.4%), and 8 of 57 patients receiving placebo (14.0%) achieved end point A1C <7.0%. The percentage of patients achieving end point A1C <7.0% was lower in patients with higher baseline A1C levels. In patients with intermediate baseline A1C levels (>7.9 but ≤8.5%), 22.2, 31.4, and 12.5% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively, achieved A1C <7.0%. In patients with higher baseline A1C levels (>8.5%), 7.5, 16.3, and 2.1% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively, achieved end point A1C <7.0%.

Baseline FPG averaged 9.7 ± 0.2, 9.9 ± 0.2, and 10.1 ± 0.2 mmol/l in patients randomized to 50 mg vildagliptin daily, 100 mg vildagliptin daily, and placebo, respectively. A dose-related decrease in FPG was also observed, and a modest increase in FPG was seen in patients receiving placebo added to metformin (AMΔ = 0.7 ± 0.2, $P = 0.002$ vs. baseline). The between-treatment difference in the AMΔ FPG at study end point was −0.8 ± 0.3 mmol/l in patients receiving 50 mg daily ($P = 0.003$) and −1.7 ± 0.3 mmol/l in those receiving 100 mg daily ($P < 0.001$).

Standard meal tests

Standard meal tests were performed in a subset of patients agreeing to participate (~30% of patients, with baseline characteristics representative of the primary ITT population). Supplemental Fig. 3 depicts plasma glucose (*A* and *B*) and insulin (*C* and *D*) during standard meal tests performed at baseline (*A* and *C*) and at study end point (*B* and *D*). At baseline, the prandial glucose profiles were similar in the three treatment groups, although glucose levels were slightly lower in patients randomized to placebo than in those randomized to either vildagliptin treatment regimen. Postprandial plasma insulin levels at baseline were very similar in patients randomized to placebo or 100 mg vildagliptin daily and somewhat lower in patients randomized to 50 mg vildagliptin daily. At week 24, or study end point, both FPG and PPG levels were lower in patients receiving either vildagliptin treatment regimen than in those receiving placebo added to metformin. At week 24 (study end point), the prandial insulin profiles were similar in each treatment group.

The AMΔs from baseline to end point in the 2-h PPG and the index of β-cell function are depicted in Fig. 1*C* and *D*, respectively. At baseline, the 2-h PPG averaged 13.8 ± 0.4, 13.5 ± 0.5, and 13.1 ± 0.5 mmol/l in patients randomized to 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. After 24-week treatment, PPG decreased significantly in vildagliptin-treated patients; the between-treatment difference in the 2-h PPG at study end point was −1.9 ± 0.6 in patients receiving 50 mg vildagliptin daily ($P = 0.001$) and −2.3 ± 0.6 mmol/l in patients who received 100 mg vildagliptin daily ($P < 0.001$).

At baseline, the β-cell function index (i.e., the ratio of the 2-h ISR AUC to the 2-h glucose AUC) averaged 18.7 ± 1.1, 20.0 ± 1.0, and 20.3 ± 1.1 pmol/min per m^2 per mmol/l in patients randomized to 50 mg vildagliptin daily, 100 mg vildagliptin daily, and placebo, respectively. After 24 weeks of treatment, these measures increased significantly in vildagliptin-treated patients; the between-treatment difference in the AMΔ in β-cell function at study end point was 5.2 ± 1.2 and 5.7 ± 1.2 pmol/min per m^2 per mmol/l in patients receiving 50 mg vildagliptin daily ($P < 0.001$) and 100 mg vildagliptin daily ($P < 0.001$), respectively.

Lipids and body weight

At baseline in the combined cohort, fasting levels of triglycerides and total, LDL, HDL, non-HDL, and VLDL cholesterol averaged 2.3 and 5.0, 2.8, 1.2, 3.8, and 1.0 mmol/l, respectively. Body weight at baseline averaged 92.5 ± 1.6, 95.3 ± 1.5, and 94.8 ± 1.8 kg in patients randomized to 50 mg vildagliptin daily, 100 mg vildagliptin daily, and placebo, respectively. Supplemental Fig. 4 depicts the AMΔ from baseline to end point in fasting lipids (*A*) and body weight (*B*). As shown in supplemental Fig. 4*A*, except for fasting triglycerides, lipid parameters changed by <3% in all treatment groups, and no significant between-treatment differences were observed. In patients receiving placebo while maintaining metformin monotherapy, fasting triglyceride levels increased by 19 ± 6%, whereas in patients receiving 50 mg vildagliptin daily, fasting triglycerides increased by 1 ± 5% ($P = 0.014$ vs. placebo), and, in patients receiving 100 mg vildagliptin daily, fasting triglycerides increased by 5 ± 5% ($P = 0.052$ vs. placebo).

As shown in supplemental Fig. 4*B*, relative to baseline, body weight did not change significantly after 24 weeks of treatment with 50 mg vildagliptin daily (AMΔ = −0.4 ± 0.3 kg) or 100 mg vildagliptin daily (AMΔ = 0.2 ± 0.3 kg), while in patients receiving placebo and continuing metformin monotherapy, body weight decreased by 1.0 ± 0.3 kg ($P < 0.001$ vs. baseline). Thus, relative to placebo, body weight was unchanged in patients receiving 50 mg vildagliptin daily, but the increase in patients receiving 100 mg vildagliptin daily (between-group difference 1.2 ± 0.4 kg) was statistically significant.

The change in body weight from baseline to study end point in the three treatment groups was also assessed by a categorical analysis and expressed as the percentage of patients experiencing a meaningful increase in body weight (>1 kg), a meaningful decrease in body weight (>1 kg), or weight neutrality (Δ body weight between −1 and 1 kg). A total of 30.8% of patients receiving either vilagliptin regimen had no meaningful change in body weight, and body weight changed by ≤1 kg in 37.7% of patients receiving placebo and continuing metformin. Weight gain of >1 kg was experienced by 31.5, 37.1, and 16.2% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. Weight loss of >1 kg was experienced by 37.8, 32.2, and 46.2% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively.

Safety and tolerability

As summarized in supplemental Table 1, during 24 weeks of treatment, one or more AEs were reported by a similar percentage of patients in each treatment group. Although there were no notable differences between treatment groups in the frequency of any specific AE, gastrointestinal AEs were significantly less frequent in patients receiving 50 mg vildagliptin daily in combination with metformin than in patients receiving placebo and metformin ($P = 0.022$, prespecified analysis). The majority of AEs reported during this study were considered to be mild or moderate and not suspected to be related to study medication.

Serious AEs (SAEs) were reported in 2.3, 2.7, and 4.4% of patients receiving 50 mg vildagliptin daily, 100 mg daily, and placebo, respectively. AEs leading to discontinuation occurred in 4.5, 4.4, and 2.2% of patients receiving 50 mg vildagliptin daily, 100 mg daily, and placebo, respectively.

The SAEs occurring in patients in the 50 mg vildagliptin treatment group were one instance each of coronary artery disease, deep venous thrombosis, acute uveitis, and renal calculus; the first three named SAEs led to discontinuation. The SAEs occurring in patients in the 100 mg vildagliptin treatment group were one instance each of silent ischemia, anginal attack, left limb acute ischemia, stroke and suspected gastrointestinal infection (in the same patient), urinary tract infection, and diarrhea with dehydration. The patient who experienced the anginal attack discontinued the study. The SAEs occurring in patients receiving placebo added to metformin were one instance each of squamous cell carcinoma of the skin, inverted T-wave, skeletal cancer, coronary artery blockage, bronchitis with exacerbated asthma, uterine fibroids, transient ischemic attack and left eye hemorrhage (in the same patient), and coronary artery disease with unstable angina pectoris. The patients with SAEs of inverted T-wave and skeletal cancer discontinued the study.

One patient in each treatment group experienced one mild hypoglycemic event. No severe (grade 2) hypoglycemic events were reported, and no deaths occurred during the study.

Both systolic and diastolic blood pressure tended to decrease during the study in each treatment group, and the decrease in diastolic blood pressure in patients receiving 100 mg vildagliptin daily (AMΔ = -2.0 ± 0.6 mmHg) was significantly greater than that in patients receiving placebo (AMΔ = -0.3 ± 0.6 mmHg, P = 0.0343).

CONCLUSIONS — This study demonstrates that the DPP-4 inhibitor vildagliptin at doses of 50 or 100 mg daily, when added to metformin monotherapy, results in a clinically significant and dose-related decrease in FPG and A1C. These effects are associated with an improvement in measures of β-cell function, with no weight gain and no increase in the incidence of hypoglycemia. Furthermore, the combination is very well tolerated with no major safety concerns identified in this study. Thus, it appears that combining vildagliptin with metformin is an effective and well-tolerated approach to treating patients with type 2 diabetes.

These results are consistent with those observed in an earlier phase II study conducted in a similar patient population (5). In the present study, the 50 mg daily dose of vildagliptin resulted in a placebo-adjusted decrease in A1C of 0.8% at week 12, and A1C remained stable for the remainder of the study. The 100 mg daily dose of vildagliptin provided additional efficacy, achieving a placebo-adjusted A1C reduction of 1.2% at week 12, with no appreciable changes in A1C thereafter. In the aforementioned phase II study, the placebo-subtracted A1C in patients receiving 50 mg vildagliptin daily added to metformin was −0.7%, and this was −1.1% after 52 weeks of treatment, reflecting deterioration of glycemic control in the patients receiving placebo and continuing metformin treatment.

Although firm conclusions cannot be drawn from comparisons between studies performed in different patient populations with different designs, the efficacy of vildagliptin added to metformin appears to be within the range of results of similar previous studies with other oral antidiabetes agents (9–13) and with the injectable incretin mimetic exenatide (14). Supplemental Table 2 summarizes these published findings.

A particularly noteworthy finding of this study is the improvement in measures of β-cell function seen in patients treated with vildagliptin. While absolute plasma insulin levels were essentially unchanged by vildagliptin treatment (see supplemental Fig. 3*C* and *D*), both vildagliptin dose regimens elicited similar, approximately threefold increases in β-cell function relative to placebo when expressed as ISR relative to glucose (Fig. 1*B*). The lack of a dose-response in this parameter describing β-cell function reflects the fact that 50 mg vildagliptin was given just before the breakfast meal test in both the 50 and 100 mg vildagliptin daily dose regimen. Indeed, essentially complete inhibition of DPP-4 is produced by either dose for >4 h (the duration of meal test sampling), as well as by doses as low as 10 mg, and it is the duration of DPP-4 inhibition that is dose related (16).

The improvement in the β-cell function index used in the present study is in agreement with previous reports demonstrating a significant effect on other measures, such as the corrected insulin response following meal tests (4). Although a variety of mechanisms may contribute to the therapeutic efficacy of DPP-4 inhibitors (15), the present findings suggest an important role for improved β-cell function.

Consistent with previous experience, vildagliptin was very well tolerated. Hypoglycemia was rarely encountered, and vildagliptin elicited no clinically meaningful mean increase in body weight despite the improvement in overall glycemic control. The observation in this study that the frequency of gastrointestinal side effects in patients receiving vildagliptin tended to be lower than that in patients receiving placebo and continuing metformin requires confirmation and further investigation. Overall, the safety profile of vildagliptin was well characterized in this study.

From this study it may be concluded that vildagliptin elicits clinically significant and dose-related decreases in FPG, PPG, and, accordingly, A1C when added to metformin monotherapy. In view of its efficacy and excellent tolerability profile, vildagliptin may be a useful addition to the therapeutic armamentarium for treatment of patients with type 2 diabetes.

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