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

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Running title: Vildagliptin added to metformin
**ABSTRACT**

**Objective:** To evaluate the efficacy and safety of vildagliptin, a new dipeptidyl peptidase-4 inhibitor, added to metformin during 24-week treatment in patients with type 2 diabetes.

**Research Design and Methods:** Double-blind, randomized, multicenter, parallel group study of 24-week treatment with vildagliptin 50 mg daily (n = 177), 100 mg daily (n = 185), or placebo (n = 182) in patients continuing a stable metformin dose regimen (≥1500 mg/day) but achieving inadequate glycemic control (HbA1c = 7.5%-11%).

**Results:** The between-treatment difference (vildagliptin – placebo) in adjusted mean change (AMΔ) in HbA1c from baseline to endpoint was -0.7 ± 0.1% (P < .001) and -1.1 ± 0.1% (P < .001) in patients receiving vildagliptin 50 mg or 100 mg daily, respectively. The between-treatment difference in the AMΔ fasting glucose (FPG) was -0.8 ± 0.3 mmol/L (P = .003) and -1.7 ± 0.3 mmol/L (P < .001) in patients receiving vildagliptin 50 mg or 100 mg daily, respectively. Adverse events (AEs) were reported by 63.3%, 65.0%, and 63.5% of patients receiving vildagliptin 50 mg daily, 100 mg daily, or placebo, respectively. Gastrointestinal AEs were reported by 9.6% (P = .022 vs placebo), 14.8%, and 18.2% of patients receiving vildagliptin 50 mg daily, 100 mg 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 HbA1c and FPG as add-on therapy in patients with type 2 diabetes inadequately controlled by metformin.

This trial (NCT00099892) is registered with ClinicalTrials.gov.
Vildagliptin is a new oral antidiabetic 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 (GLP-1). Early studies suggest that vildagliptin improves islet function in patients with type 2 diabetes (T2DM) 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 T2DM was shown to decrease fasting (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 improve glycemic control in patients with T2DM (5).

Metformin is the most commonly prescribed first-line antidiabetic drug worldwide, but due to the progressive worsening of blood glucose control during the natural history of T2DM, 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 T2DM inadequately controlled with metformin monotherapy.

RESEARCH DESIGN AND METHODS

Study design. This was a 24-week, double-blind, randomized, placebo-controlled, parallel-group study conducted at 109 centers in the US (79), France (8), Italy (6), and Sweden (16). Patients with T2DM 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 vildagliptin 50 mg daily (as a qd dose), 100 mg daily (as equally divided doses), or placebo. Efficacy and tolerability were assessed during 4 additional visits, at Weeks 4, 12, 16, and 24 of treatment.

Study population. The study enrolled patients with T2DM who had been treated with metformin monotherapy for at least 3 months and who had been on a stable dose of ≥1500 mg daily for a minimum of 4 weeks prior to Visit 1. Participants were required to have HbA1c in the range of 7.5% to 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 2000 mg daily at Visit 1. Male and female patients (non-fertile or of childbearing potential using a medically approved birth control method) aged 18 to 78 years, inclusive, with a BMI in the range of 22 to 45 kg/m², 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 diabetic 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 suggested by elevated serum creatinine levels ≥132 µmol/L for males, ≥123 µmol/L for females.

Study assessments. HbA1c, 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 (TG, total, LDL, HDL, non-HDL, and VLDL cholesterol) were measured and ECGs were performed at screening and at Weeks 0, 12, and 24. Standard breakfast meal tests (500 kcal; 60% CHO, 30% fat, 10% protein) were performed at Week 0 and Week 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-hour area under the curve (AUC) 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 (SMBG) 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 HbA1c were performed by Bioanalytical Research Corporation (BARC). Assays were performed according to standardized and validated procedures according to Good Laboratory Practice. HbA1c measurements were performed by either BARC-EU (Ghent, Belgium) for European subjects or by the National Glycohemoglobin Standardization Program (NGSP) network laboratory, Diabetes Diagnostics Laboratory (DDL, Columbia, MO), or Covance-US (Indianapolis, IN) for US subjects. All samples from any single patient were measured by the same laboratory.

Data analysis. The primary efficacy variable was the change from baseline in HbA1c at study endpoint using last observation carried forward (LOCF) 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 1) had a reliable screening HbA1c value ≥7.4%, 2) received at least one dose of study medication, and 3) had a reliable baseline and at least one reliable post-baseline HbA1c measurement. This population is referred to as the primary intent-to-treat (ITT) population and was pre-specified as the main efficacy population. Changes from baseline in primary and secondary endpoints 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 2-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 exposed to at least one dose of study drug and had at least one post-baseline safety assessment.

Ethics and good clinical practice. All participants provided written informed consent. The protocol was approved by the independent ethics 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
Patients studied. Patient disposition from screening through study endpoint is summarized in online appendix Figure 1 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
more than 83% of patients in each treatment group completed the study. In the primary ITT population, the groups were well balanced at baseline, with HbA1c 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 ~2100 mg/day. Standard breakfast meal test was performed at week 0 and week 24 in a subgroup of 163 patients with characteristics representative of the whole ITT population, 53 in the vildagliptin 50 mg daily, 56 in the vildagliptin 100 mg daily, and 54 in the placebo treated groups.

**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 HbA1c and FPG during 24-week treatment with vildagliptin 50 mg daily, 100 mg daily, or placebo added to metformin are depicted in Figure 2 (Panels A and B, respectively). The mean baseline HbA1c was 8.4 ± 0.1% in both groups of patients randomized to vildagliptin and 8.3 ± 0.1% in patients randomized to placebo. The AMΔ HbA1c was 0.2 ± 0.1% in patients receiving placebo and -0.5 ± 0.1 and -0.9 ± 0.1% in patients receiving vildagliptin 50 mg and 100 mg daily, respectively. The between-treatment difference (vildagliptin – placebo) was -0.7 ± 0.1% with vildagliptin 50 mg daily and 100 mg daily, respectively. The response to treatment, online appendix Figure 2 (available at http://dx.doi.org/10.2337/dc06-1732) depicts the number of patients in each treatment group who experienced a deterioration of glycemic control (Δ HbA1c > 0.3%), no meaningful change (Δ HbA1c = -0.3 to 0.3%), a moderate improvement (Δ HbA1c = -0.4 to -1.0%) or a marked improvement (Δ HbA1c = -1.1 to -2.0%, or Δ HbA1c < -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 1/3 of patients. In contrast, in the group receiving vildagliptin 50 mg daily, >2/3 of patients experienced meaningful (37.8%) or marked (29.4%) improvement in glycemic control. In the group receiving vildagliptin 100 mg daily and continuing metformin treatment, more than ¾ of patients experienced a meaningful (41.3%) or marked (37.1%) improvement in glycemic control.

Responder rates (percentage of patients achieving endpoint HbA1c < 7.0%) were also calculated and stratified according to baseline HbA1c level. In patients with baseline HbA1c ≤ 7.9%, 26 of 52 patients receiving vildagliptin 50 mg daily (50.0%), 31 of 57 patients receiving vildagliptin 100 mg daily (54.4%) and 8 of 57 patients receiving placebo (14.0%) achieved endpoint HbA1c < 7.0%. The percentage of patients achieving endpoint HbA1c < 7.0% was lower in patients with higher baseline HbA1c levels. In patients with intermediate baseline HbA1c levels (> 7.9% but ≤ 8.5%), 22.2%, 31.4% and 12.5% of patients receiving vildagliptin 50 mg daily, 100 mg daily, respectively, achieved endpoint HbA1c < 7.0%. In patients with higher baseline HbA1c levels (> 8.5%), 7.5%, 16.3% and 2.1% of patients receiving vildagliptin 50 mg daily, 100 mg daily, respectively, achieved endpoint HbA1c < 7.0%.

Baseline FPG averaged 9.7 ± 0.2, 9.9 ± 0.2, and 10.1 ± 0.2 mmol/L in patients randomized to vildagliptin 50 mg daily, 100 mg 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 endpoint was -0.8 ± 0.3 mmol/L in patients receiving 50 mg daily (P = .003) and -1.7 ± 0.3 mmol/L in those receiving 100 mg daily (P < .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). Online appendix Figure 3 depicts plasma glucose (Panels A and B) and insulin (Panels C and D) during standard meal tests performed at baseline (Panels A and C) and at study endpoint (Panels 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 vildagliptin 100 mg daily and somewhat lower in patients randomized to vildagliptin 50 mg daily. At Week 24 or study endpoint, both fasting and postprandial glucose levels were lower in patients receiving either vildagliptin treatment regimen than in those receiving placebo added to metformin. At Week 24 or study endpoint the prandial insulin profiles were similar in each treatment group.

The adjusted mean change from baseline to endpoint in the 2-hour postprandial glucose (2-h PPG) and the index of β-cell function are depicted in Figure 1 (Panels 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 vildagliptin 50 mg daily, 100 mg daily, and placebo, respectively. After 24-week treatment, postprandial glucose decreased significantly in vildagliptin-treated patients: the between-treatment difference in the 2-h PPG at study endpoint was -1.9 ± 0.6 in patients receiving vildagliptin 50 mg daily (P = .001) and -2.3 ± 0.6 mmol/L in patients who received vildagliptin 100 mg daily (P < .001).

At baseline the β-cell function index (ie, the ratio of the 2-hour AUC for the insulin secretory rate (ISR) to the 2-hour AUC for glucose) averaged 18.7 ± 1.1, 20.0 ± 1.0, and 20.3 ± 1.1 pmol/min/m²/mmol/L in patients randomized to vildagliptin 50 mg daily, 100 mg daily, and placebo, respectively. After 24-week treatment, these measures increased significantly in vildagliptin-treated patients; the between-treatment difference in the AMΔ in β-cell function at study endpoint was 5.2 ± 1.2 and 5.7 ± 1.2 pmol/min/m²/mmol/L in patients receiving vildagliptin 50 mg daily, 100 mg daily, and placebo, respectively.

**Lipids and body weight.** At baseline in the combined cohort, fasting levels of TG, total, LDL, HDL, non-HDL, and VLDL cholesterol averaged 2.3, 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 vildagliptin 50 mg daily, 100 mg daily, and placebo, respectively. Figure 5 depicts the adjusted mean change from baseline to endpoint in fasting lipids (Panel A) and body weight (Panel B). As shown in online appendix Figure 4A, except for fasting TG, lipid parameters changed by less than 3% in all treatment groups and no significant between-treatment differences were observed. In patients receiving placebo while maintaining metformin monotherapy, fasting TG levels increased by 19 ± 6% whereas in patients receiving vildagliptin 50 mg daily, fasting TG increased by 1 ± 5% (P = .014 vs placebo) and in patients receiving vildagliptin 100 mg daily, fasting TG increased by 5 ± 5% (P = .052 vs placebo).

As shown in online appendix Figure 4B, relative to baseline, body weight did not change significantly after 24-week treatment with vildagliptin 50 mg daily (AMΔ = -0.4 ±
0.3 kg) or 100 mg 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 < .001 vs baseline). Thus relative to placebo, body weight was unchanged in patients receiving vildagliptin 50 mg daily, but the increase in patients receiving vildagliptin 100 mg daily (between-group difference = 1.2 ± 0.4 kg) was statistically significant.

The change in body weight from baseline to study endpoint 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 vildagliptin 50 mg daily, 100 mg daily or placebo, respectively. Weight loss of >1 kg was experienced by 37.8%, 32.2% and 46.2% of patients receiving vildagliptin 50 mg daily, 100 mg daily or placebo.

Safety and tolerability. As summarized in online appendix Table 2, during 24-week 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 vildagliptin 50 mg daily in combination with metformin than in patients receiving placebo and metformin (P = .022, pre-specified 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 were reported in 2.3%, 2.7%, and 4.4% of patients receiving vildagliptin 50 mg daily, 100 mg daily, and placebo, respectively. Adverse events leading to discontinuation occurred in 4.5%, 4.4%, and 2.2% of patients receiving vildagliptin 50 mg daily, 100 mg daily, and placebo, respectively.

The SAEs occurring in patients in the vildagliptin 50 mg 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 vildagliptin 100 mg daily 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 from 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 from 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 vildagliptin 100 mg daily (AMΔ = -2.0 ± 0.6 mm Hg) was significantly greater than that in patients receiving placebo (AMΔ = -0.3 ± 0.6 mm Hg, P = .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 HbA1c. 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 T2DM.

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 HbA1c of 0.8% at Week 12, and HbA1c remained stable for the remainder of the study. The 100 mg daily dose provided additional efficacy, achieving a placebo-adjusted reduction of 1.2% at Week 12, with no appreciable changes in HbA1c thereafter. In the aforementioned Phase II study, the placebo-subtracted HbA1c in patients receiving vildagliptin 50 mg daily added to metformin was -0.7% and this was -1.1% after 52-week 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 antidiabetic agents (9-13) and with the injectable incretin mimetic, exenatide (14). Online appendix 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 (cf online appendix Figure 3C and D) both vildagliptin dose regimens elicited similar, ~3-fold increases in β-cell function relative to placebo when expressed as insulin secretory rate relative to glucose (cf Figure 1B). The lack of a dose-response in this parameter describing β-cell function reflects the fact that 50 mg vildagliptin was given just prior to the breakfast meal test in both the 50 mg daily and the 100 mg daily dose regimen. Indeed, essentially complete inhibition of DPP-4 is produced by either dose for > 4 hours (the duration of meal test sampling) is produced by doses as low as 10 mg and it is the duration of DPP-4 inhibition that is dose related (Y-L He, et al, submitted).

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 (1415), 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, HbA1c 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.

ACKNOWLEDGMENTS
The authors gratefully acknowledge the investigators and staff at the 109 participating centers, and the editorial assistance of Beth Dunning Lower, PhD. This study was funded by Novartis Pharmaceuticals Corporation. A list of investigators is provided in the Appendix.
REFERENCES


### Table 1: Patients studied and baseline characteristics of the primary ITT population

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<td>Primary ITT population</td>
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<tr>
<td>Meal test participants</td>
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**Primary ITT population** – mean ± SD or n (%)

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<th>Vildagliptin 100 mg daily</th>
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Figure 1 A and B: Mean (± SE) HbA1c (Panel A) and FPG (Panel B) during 24-week treatment with vildagliptin 50 mg daily (open triangles), 100 mg daily (closed triangles), or placebo (open circles) in patients with T2DM continuing stable metformin dose regimen (≥1500 mg/day).
Appendix: List of Investigators

France:  P Darmon, R Duhirel, M Levy, A Penfornix, M Remigy, AM Sandinini, C LeDevehat, R Mira

Italy:   F Pacini, E Bosi, G Testa, A Colao, W Donadon, F Mollo


United States:  