Effects of the Dipeptidyl Peptidase-IV Inhibitor Vildagliptin on Incretin Hormones, Islet Function, and Postprandial Glycemia in Subjects With Impaired Glucose Tolerance

JULIO ROSENSTOCK, MD[1]
JAMES E. FOLEY, PHD[2]
MARC RENDELL, MD[3]
MONA LANDIN-OLSSON, MD, PHD[4]
JENS J. HOLST, MD[5]
CAROLYN F. DEACON, PHD[5]
ERIKA ROCHOTTE, MSC[6]
MICHELLE A. BARON, MD[2]

OBJECTIVE — This study was conducted to determine the effects of vildagliptin on incretin hormone levels, islet function, and postprandial glucose control in subjects with impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — A 12-week, double-blind, randomized, parallel-group study comparing vildagliptin (50 mg q.d.) and placebo was conducted in 179 subjects with IGT (2-h glucose 9.1 mmol/l, A1C 5.9%). Plasma levels of intact glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), glucose, insulin, C-peptide, and glucagon were measured during standard meal tests performed at baseline and at week 12. Insulin secretory rate (ISR) was estimated by C-peptide deconvolution. The between-group differences (vildagliptin − placebo) in the adjusted mean changes from baseline to end point in the total and incremental (Δ) area under the curve $(AUC)_{0-2\ h}$ for these analytes were assessed by ANCOVA; glucose $AUC_{0-2\ h}$ was the primary outcome variable.

RESULTS — Relative to placebo, vildagliptin increased GLP-1 (ΔAUC, $+6.0 \pm 1.2$ pmol·l^{-1}·h^{-1}, $P < 0.001$) and GIP (ΔAUC, $+46.8 \pm 5.4$ pmol·l^{-1}·h^{-1}, $P < 0.001$) and decreased glucagon (ΔAUC, -3.0 ± 1.0 pmol·l^{-1}·h^{-1}, $P = 0.003$). Although postprandial insulin levels were unaffected (ΔAUC, $+20.8 \pm 35.7$ pmol·l^{-1}·h^{-1}, $P = 0.561$), prandial glucose excursions were reduced (ΔAUC, -1.0 ± 0.3 mmol·l^{-1}·h^{-1}, $P < 0.001$), representing an ~30% decrease relative to placebo. β-Cell function as assessed by the ISR $AUC_{0-2\ h}$/glucose $AUC_{0-2\ h}$ was significantly increased ($+6.4 \pm 2.0$ pmol·min^{-1}·m^{-2}·mmol·l^{-1}, $P = 0.002$). Adverse event profiles were similar in the two treatment groups, and no hypoglycemia was reported.

CONCLUSIONS — The known effects of vildagliptin on incretin levels and islet function in type 2 diabetes were reproduced in subjects with IGT, with a 32% reduction in postprandial glucose excursions and no evidence of hypoglycemia or weight gain.

Diabetes Care **31:30–35, 2008**

From the [1]Dallas Diabetes and Endocrine Center, Dallas, Texas; [2]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; the [3]Creighton Diabetes Center, Omaha, Nebraska; [4]University Hospital, Lund, Sweden; the [5]Panum Institute, University of Copenhagen, Copenhagen, Denmark; and [6]Novartis Pharma AG, Basel, Switzerland.

Address correspondence and reprint requests to Michelle A. Baron, MD, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936. E-mail: michelle.baron@novartis.com.

Received for publication 15 August 2007 and accepted in revised form 11 October 2007.

Published ahead of print at http://care.diabetesjournals.org on 18 October 2007. DOI: 10.2337/dc07-1616. Clinical trial reg. no. NCT00237250, clinicaltrials.gov.

J.R. has received grant support and honoraria for serving on advisory boards from Novartis.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc07-1616.

Abbreviations: AUC, area under the curve; DPP-4, dipeptidyl peptidase-IV; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; PPG, prandial glucose level.

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

Vildagliptin is a potent and selective dipeptidyl peptidase-IV (DPP-4) inhibitor that improves glycemic control in patients with type 2 diabetes (1–3) through incretin-hormone–mediated increases in both α- and β-cell responsiveness to glucose (4,5). However, vildagliptin does not affect insulin secretion or glucose tolerance in normoglycemic subjects (6), raising the question of whether a DPP-4 inhibitor could improve glycemic control in subjects with impaired glucose tolerance (IGT), in whom the incretin effect does not appear to be markedly impaired, despite other manifestations of β-cell dysfunction (7).

Pre-diabetes (i.e., IGT and/or impaired fasting glucose [IFG]) is a topic of much current interest, and it is with great hope that many diabetes prevention trials have been undertaken to determine whether treatment of pre-diabetes with oral antidiabetic agents can prevent the development of type 2 diabetes (8–10). Although it has been shown that metformin (9), rosiglitazone (10), and acarbose (8) can delay the diagnosis of type 2 diabetes, all of these agents have drawbacks in terms of tolerability and adverse event profile, and no agent has been found to modify the disease process.

In this regard, incretin-based therapies hold considerable promise because of the potential to increase β-cell mass suggested by preclinical studies with glucagon-like peptide 1 (GLP-1), exenatide, and DPP-4 inhibitors (11). However, before large and long-term diabetes prevention trials with a new oral agent such as vildagliptin, it is important to determine whether DPP-4 inhibitors can enhance the incretin system and improve glucose homeostasis in a pre-diabetic population. Accordingly, the present 12-week, multicenter, randomized, placebo-controlled study was undertaken to assess the tolerability and the effects of vildagliptin (50 mg q.d.) on incretin hormone levels, islet function, fasting and postprandial glu-

cose control, and A1C levels in subjects with IGT.

RESEARCH DESIGN AND METHODS

This was a 12-week, double-blind, randomized, placebo-controlled, parallel-group study conducted in 28 sites in the U.S. (10), Spain (5), Finland (4), the U.K. (4), Sweden (3), and Germany (2). Each subject attended a prescreening visit (week −4) during which a 75-g oral glucose tolerance test (OGTT) was performed to determine eligibility. Subjects with confirmed IGT then attended the screening visit at week −2 during which inclusion/exclusion criteria were assessed. Eligible subjects were randomly assigned at week 0 (visit 3) to receive vildagliptin (50 mg q.d.) or placebo and attended two additional study visits at weeks 4 and 12.

The study enrolled male and female subjects aged 18–80 years with IGT (FPG <7.0 mmol/l and 2-h postchallenge glucose ≥7.8 but <11.1 mmol/l) and BMI of 23–45 kg/m^2. Females with childbearing potential were required to use a medically approved birth control method. Subjects were excluded if they had diabetes (other than a history of gestational diabetes), a history of serious cardiovascular disease, liver disease such as cirrhosis or chronic active hepatitis, or significant renal dysfunction. Any of the following laboratory abnormalities also precluded participation: alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, direct bilirubin >1.3 times the upper limit of normal, serum creatinine levels ≥220 μmol/l, clinically significant thyroid-stimulating hormone values outside the normal range, or fasting triglyceride levels >7.9 mmol/l.

Study assessments

Standard breakfast meal tests (500 kcal; 60% carbohydrate, 30% fat, and 10% protein) were performed after an overnight fast at baseline (week 0) and at week 12 (or study end point). Study medication was not given before the meal test at baseline but was given 15 min before the meal at week 12. Samples for determination of active GLP-1 and gastric inhibitory polypeptide (GIP), glucose, insulin, C-peptide, and glucagon were obtained at times −20, 0, 15, 30, 60, 90, and 120 min, with the meal beginning immediately after the time 0 sample and consumed within 15 min. A1C was measured at weeks 0 and 12; FPG was measured at −2, 0, 4, and 12 weeks.

Body weight and vital signs were measured at each study visit, and standard hematology and biochemistry laboratory assessments were performed at screening (week −2), week 0, and week 12. All adverse events were recorded and assessed as to their severity and possible relationship to the study medication as judged by the investigator. Subjects 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.

GLP-1 was measured at Wuxi PharmaTech (Shanghai, China) by enzyme-linked immunosorbent assay with NH_2-terminally directed antisera. GIP was measured at the Panum Institute (Copenhagen, Denmark) by a radioimmunoassay with an antibody (code 98171) specific for the NH_2-terminus (12). Accordingly, the intact, biologically active forms of the incretin hormones were measured. All other laboratory assessments were made by Covance (Indianapolis, IN, and Geneva, Switzerland). Assays were performed according to standardized and validated procedures according to good laboratory practice.

Data analysis

Insulin secretory rate (ISR) was estimated by deconvolution of C-peptide levels and expressed per square meter of body surface area (13). The total and incremental (Δ) areas under the curve (AUC) for GLP-1, GIP, glucose, insulin, glucagon, C-peptide, and ISR were calculated with the trapezoidal method for the 0- to 2-h postmeal time interval. Insulin secretion relative to glucose (ISR $AUC_{0-2\ h}$/glucose $AUC_{0-2\ h}$) was calculated as a measure of β-cell function. In addition, homeostasis model assessment of insulin resistance (HOMA-IR) and the meal-derived insulin sensitivity index (ISI) were calculated. The primary efficacy variable was the change from baseline to end point (week 12 or last available postbaseline value) in the prandial plasma glucose $AUC_{0-2\ h}$. This and all other variables were analyzed with an ANCOVA model with treatment and predefined pooled center as the clas-

Table 1—*Baseline demographics, background characteristics, and disposition of randomly assigned patients*

	Vildagliptin, 50 mg q.d.	Placebo
n	90	89
Age	57.1 ± 10.7	59.8 ± 11.5
<65 years	62 (68.9)	51 (57.3)
≥65 years	28 (31.1)	38 (42.7)
Male sex	43 (47.8)	38 (42.7)
Race		
Caucasian	81 (90.0)	80 (89.9)
Hispanic or Latino	4 (4.4)	7 (7.9)
Black	3 (3.3)	1 (1.1)
All other	2 (2.2)	1 (1.1)
BMI	31.7 ± 4.8	30.9 ± 5.3
BMI <30 kg/m^2	39 (43.3)	45 (50.6)
BMI ≥30 kg/m^2	51 (56.7)	44 (49.4)
BMI ≥35 kg/m^2	22 (22.4)	19 (21.3)
A1C (%)	5.9 ± 0.5	5.9 ± 0.4
FPG (mmol/l)	6.2 ± 0.7	6.1 ± 0.7
2-h glucose (mmol/l) (OGTT)	9.1 ± 0.9	9.2 ± 0.9
Pre-diabetic status		
Isolated IGT	15 (16.7)	18 (20.2)
IGT plus IFG	75 (83.3)	71 (79.8)
Completed	84 (93.3)	84 (94.4)
Discontinued	6 (6.7)	5 (5.6)
Adverse event	3 (3.3)	2 (2.2)
Protocol violation	1 (1.1)	2 (2.2)
Withdrew consent	1 (1.1)	1 (1.1)
Lost to follow-up	1 (1.1)	0

Data are means ± SD or *n* (%)

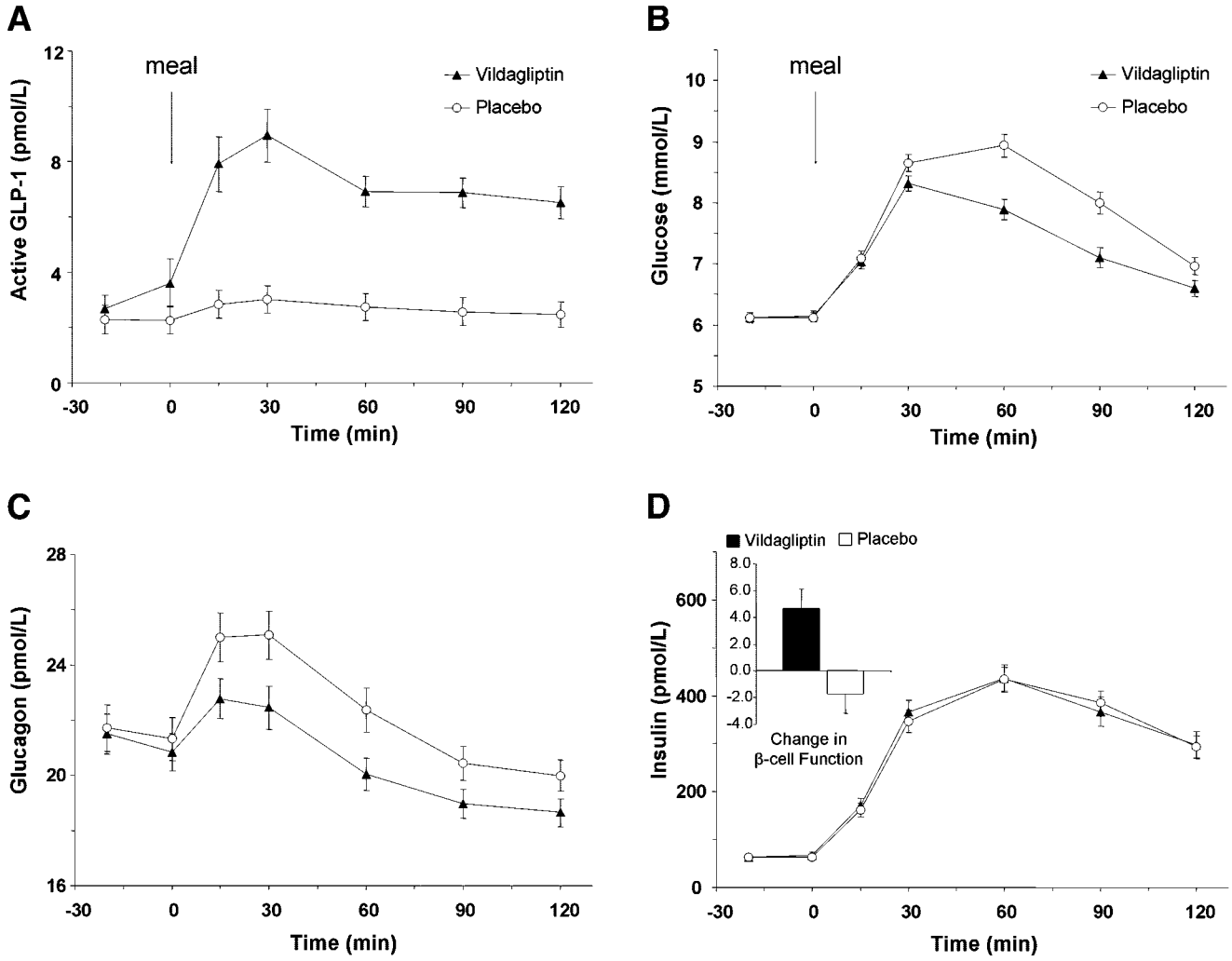

Figure 1—*Plasma levels of active GLP-1 (*A*), glucagon (*B*), glucose (*C*), and insulin (*D*) at study end point during standard meal tests performed in subjects with IGT receiving vildagliptin (50 mg q.d., ▲) or placebo (○). Mean ± SE,* n *= 89 subjects per group (intention-to-treat population).* D: Inset *shows the adjusted mean change in ISR $AUC_{0-2\ h}$/glucose $AUC_{0-2\ h}$ in subjects receiving vildagliptin or placebo.*

sification variables and baseline value as the covariate, using two-sided tests and a statistical significance level of 0.05. Prespecified subanalyses of the primary outcome variable were also performed based on baseline BMI (<30, ≥30, and ≥35 kg/m^2), age-group (<65 and ≥65 years), and sex.

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 in accordance with the Declaration of Helsinki using good clinical practice.

RESULTS — Table 1 reports the baseline demographics, metabolic characteristics, and disposition of all randomly assigned patients. The groups were well balanced at baseline, with A1C averaging 5.9% and FPG averaging 6.1 mmol/l. Subjects were predominantly Caucasian and obese, and ~80% had IFG as well as IGT. A similarly high percentage of patients in each treatment group (>90%) completed the study, and the reasons for discontinuations were similar for the two groups. Further details regarding patient flow from screening to end point are provided in Fig. 1 of the online appendix (available at http://dx.doi.org/10.2337/dc07-1616).

Incretin hormones, pancreatic hormones, and glucose during standard meal tests

Figure 1 depicts plasma levels of active GLP-1, glucagon, insulin, and glucose at study end point. The hormone and glucose profiles during standard meal tests performed at baseline were very similar in the two groups and are not depicted. As shown in Fig. 1*A*, in subjects receiving placebo, active GLP-1 increased very modestly after food intake, whereas there was a marked and sustained increase in active GLP-1 in vildagliptin-treated subjects. This was also the case for plasma levels of active GIP (Fig. 2 of the online appendix). Plasma glucagon levels were substantially suppressed during the high-carbohydrate meal in subjects receiving vildagliptin relative to those receiving placebo (Fig. 1*B*). As shown in Fig. 1*C*, glucose levels increased after the meal in subjects receiving placebo and to a lesser degree in those receiving vildagliptin, and postmeal plasma insulin levels were superimposable in the two groups of subjects (Fig. 1*D*). However, as illustrated in the inset of Fig. 1*D*, insulin secretion relative to that of glucose (β-cell function)

Table 2—*Statistical analysis of meal test–derived parameters, FPG, A1C, and body weight in the intention-to-treat population*

	n	Baseline	Adjusted mean change	Between-group difference	*P*
GLP-1 $AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	73	5.7 ± 1.2	8.5 ± 0.7	8.8 ± 1.0	<0.001
Placebo	74	6.0 ± 1.1	−0.3 ± 0.7		
GLP-1 $\Delta AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	73	1.1 ± 0.2	5.8 ± 0.8	6.0 ± 1.2	<0.001
Placebo	74	0.9 ± 0.3	−0.2 ± 0.8		
GIP $AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	47	41.7 ± 2.3	53.2 ± 4.3	51.3 ± 5.4	<0.001
Placebo	50	50.9 ± 3.2	1.8 ± 4.5		
GIP $\Delta AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	47	25.1 ± 2.1	41.3 ± 4.3	46.8 ± 5.4	<0.001
Placebo	50	33.8 ± 3.0	−5.5 ± 4.5		
Glucagon $AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	79	43.1 ± 1.2	−1.9 ± 0.8	-3.3 ± 1.2	0.007
Placebo	76	43.7 ± 1.4	1.4 ± 0.8		
Glucagon $\Delta AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	79	1.7 ± 0.7	−2.8 ± 0.8	-3.0 ± 1.0	0.003
Placebo	76	2.2 ± 0.7	0.2 ± 0.7		
Insulin $AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	74	653 ± 43	−29.4 ± 26.2	36.8 ± 37.4	0.327
Placebo	73	750 ± 52	−66.1 ± 26.8		
Insulin $\Delta AUC_{0-2\ h}$ (pmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	74	524 ± 37	−37.6 ± 25.0	20.8 ± 35.7	0.561
Placebo	73	619 ± 45	-58.4 ± 25.6		
Glucose $AUC_{0-2\ h}$ (mmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	83	15.8 ± 0.3	−0.9 ± 0.2	-1.0 ± 0.3	<0.001
Placebo	82	15.9 ± 0.3	0.1 ± 0.2		
Glucose $\Delta AUC_{0-2\ h}$ (mmol · l^{-1} · h^{-1})					
Vildagliptin 50 mg q.d.	83	3.2 ± 0.2	−0.7 ± 0.2	-1.0 ± 0.3	<0.001
Placebo	82	3.5 ± 0.2	0.3 ± 0.2		
Peak prandial glucose excursion (mmol/l)					
Vildagliptin 50 mg q.d.	85	3.0 ± 0.1	−0.6 ± 0.1	−0.6 ± 0.2	<0.001
Placebo	85	3.3 ± 0.1	0.1 + 0.1		
2-h postprandial plasma glucose level (mmol/l)					
Vildagliptin 50 mg q.d.	84	6.8 ± 0.2	−0.2 ± 0.1	−0.3 ± 0.2	0.067
Placebo	82	6.8 ± 0.1	0.1 ± 0.1		
Insulin secretion relative to glucose (ISR $AUC_{0-2\ h}$/ glucose $AUC_{0-2\ h}$ [pmol · min^{-1} · m^{-2} · mmol · l^{-1}])					
Vildagliptin 50 mg q.d.	76	58.6 ± 2.0	4.7 ± 1.4	6.4 ± 2.0	0.002
Placebo	76	60.4 ± 2.2	-1.7 ± 1.5		
FPG (mmol/l)					
Vildagliptin 50 mg q.d.	89	6.18 ± 0.08	−0.03 ± 0.06	−0.04 ± 0.08	0.660
Placebo	89	6.10 ± 0.08	0.00 ± 0.06		
A1C (%)					
Vildagliptin 50 mg q.d.	85	5.93 ± 0.06	−0.13 ± 0.03	−0.15 ± 0.04	<0.001
Placebo	78	5.89 ± 0.05	0.02 ± 0.03		
Body weight (kg)					
Vildagliptin 50 mg q.d.	89	87.1 ± 1.5	−0.6 ± 0.2	−0.5 ± 0.3	0.125
Placebo	89	86.9 ± 1.8	−00.1 ± 0.2		

Data are means ± SEM.

increased in vildagliptin-treated subjects and decreased modestly in subjects receiving placebo.

Table 2 summarizes the statistical comparisons of the total and incremental (suprabasal [Δ]) AUCs for incretin hormones, pancreatic hormones, and plasma glucose, as well as peak prandial glucose excursion, 2-h postprandial glucose level (PPG), and insulin secretion relative to that of glucose in subjects receiving vildagliptin or placebo. Relative to placebo, vildagliptin significantly increased the $AUC_{0-2\ h}$ and $\Delta AUC_{0-2\ h}$ for active GLP-1 and GIP and significantly de-

creased both the $AUC_{0-2\ h}$ and the $\Delta AUC_{0-2\ h}$ for glucagon and glucose. The increase in the ΔAUCs for GLP-1 and GIP represented >5- and nearly 2-fold increases, respectively. The ΔAUC for glucose decreased by ~22% in vildagliptin-treated subjects and increased by ~8% in those receiving placebo; thus, relative to placebo, vildagliptin decreased the glucose ΔAUC by ~30%. There was a modest but significant decrease in the peak prandial glucose excursion (between-group difference of −0.6 mmol/l), but the decrease in postmeal 2-h PPG (between-treatment difference of −0.3 mmol/l) did not reach statistical significance.

Subgroup analyses of prandial glucose control and measures of insulin resistance

Baseline BMI, age, and sex did not appear to influence the efficacy of vildagliptin to reduce postprandial glucose levels. In patients receiving vildagliptin, the mean changes from baseline in glucose $AUC_{0-2\ h}$ were similar in nonobese (-0.9 ± 0.3 mmol · l^{-1} · h^{-1}), obese (-0.8 ± 0.3 mmol · l^{-1} · h^{-1}), and severely obese (-0.8 ± 0.5 mmol · l^{-1} · h^{-1}) subjects; in younger (-0.9 ± 0.3 mmol · l^{-1} · h^{-1}) and older (-0.7 ± 0.3 mmol · l^{-1} · h^{-1}) subjects; and in men (-0.8 ± 0.3 mmol · l^{-1} · h^{-1}) and women (-0.9 ± 0.3 mmol · l^{-1} · h^{-1}).

At baseline, HOMA-IR averaged 2.6 ± 0.2 in patients randomly assigned to vildagliptin and 2.8 ± 0.2 in those randomly assigned to placebo. HOMA-IR decreased during the 12-week treatment with vildagliptin (-0.2 ± 0.1) and to a somewhat lesser extent in patients receiving placebo (-0.1 ± 0.1); however, the between-group difference (-0.1 ± 0.2) was not statistically significant ($P = 0.613$). At baseline, the ISI averaged 5.2 ± 0.4 in patients randomly assigned to vildagliptin and 4.6 ± 0.3 in those randomly assigned to placebo. The ISI increased during the 12-week treatment with vildagliptin ($+0.5 \pm 0.2$) and to a somewhat lesser degree in patients receiving placebo (0.2 ± 0.2). However, the between-treatment difference in the adjusted mean change from baseline in ISI (0.2 ± 0.3) was not statistically significant ($P = 0.485$).

FPG, A1C, and body weight

The FPG at baseline was similar in the two treatment groups and did not change significantly by study end point. Baseline A1C was 5.9% in both treatment groups, and relative to placebo, this decreased significantly (−0.15%) during vildagliptin treatment ($P < 0.001$). Body weight was similar at baseline in the two treatment groups, and there was a nonsignificant trend for weight reduction in the vildagliptin treatment group.

Tolerability

One or more adverse events was reported by 49 subjects receiving vildagliptin (54.4%) and by 44 subjects receiving placebo (49.4%). No hypoglycemia was reported. A summary of the most common specific adverse events is provided in Table 1 of the online appendix. No specific adverse event occurred in more than four subjects in either group, and there were no notable differences in the adverse event profiles in subjects receiving vildagliptin or placebo. There was one serious adverse event in the vildagliptin group (congestive heart failure) and two serious adverse events in the placebo group (one instance of appendicitis and one instance of cellulitis). There were three discontinuations due to an adverse event in the vildagliptin group (two instances of headache and one instance of hypoesthesia) and two discontinuations due to an adverse event in the placebo group (one instance each of bronchospasm and eczema). There were no major changes from baseline to end point or between-treatment differences at end point for any biochemistry, hematology, or urinalysis parameter or vital sign, and no consistent trends over time were noted.

CONCLUSIONS — The present work provides the first evidence regarding the effects of a DPP-4 inhibitor in a pre-diabetic population. This study clearly established the fact that the mechanisms underlying the clinical efficacy of vildagliptin in patients with type 2 diabetes are also operant in pre-diabetes, as demonstrated by markedly increased postprandial incretin hormone responses of >5- and nearly 2-fold increases in the incremental AUCs for GLP-1 and GIP, respectively. These effects were associated with improvements in both β-cell function (increased insulin secretion relative to glucose) and α-cell function as measured by a reduction in the inappropriate glucagon release in response to a high-carbohydrate meal and, consequently, decreased prandial glucose excursions (~30% reduction in ΔAUC for glucose). Twelve-week treatment with vildagliptin also modestly but significantly decreased A1C despite normal baseline levels, although there was no effect on FPG.

The findings of the present study in pre-diabetes regarding incretin hormones and islet function agree qualitatively with earlier studies performed in patients with type 2 diabetes, although quantitative comparisons are problematic because of differences in experimental design. Thus, in all studies in which meal tests were performed, vildagliptin greatly increased postmeal plasma levels of active GLP-1 (4,14) and GIP (4,14), decreased inappropriate glucagon secretion (4,14), and increased insulin secretion relative to glucose (4) as well as other measures of β-cell function (14,15), irrespective of dose used, treatment duration, or concomitant oral antidiabetic medication.

Vildagliptin has now been studied in a very broad spectrum of subjects, from those with pre-diabetes to patients with diabetes and mild hyperglycemia (16). It also has been studied in drug-naive patients with type 2 diabetes and moderate to severe hyperglycemia (2,3,17) and as an add-on to metformin (18), pioglitazone (19), or insulin (20). In all of these studies, vildagliptin decreased FPG, PPG, and A1C, and the magnitude of the change was proportional to the baseline value. Indeed, the effects of vildagliptin on measures of glycemic control in this study were proportional to the degree of dysregulation exhibited by the IGT study population. The reduction in A1C, although modest (a decrease of 0.15% from a baseline of 5.9%), is noteworthy because it is known that A1C correlates with total, cardiovascular disease, and ischemic heart disease mortality even within the range of normal levels (21).

Although vildagliptin has been reported to improve measures of insulin sensitivity in patients with type 2 diabetes (14), the modest trends toward decreased HOMA-IR and increased ISI observed in the present study were not statistically significant compared with placebo. This finding is probably explained by the very modest degree of hyperglycemia in the study participants, the lack of effect on FPG, and the fact that these subjects with IGT were not exceptionally insulin resistant at baseline (fasting insulin levels <70 pmol/l) (Fig. 1*D*).

OGTTs were performed initially (before study randomization) only to ascertain the glucose tolerance status of the study participants; this was assessed with a more physiological meal test during the study. Perhaps it may be perceived as a

limitation of the present study that a repeat OGTT was not performed at the study end point to determine whether this DPP-4 inhibitor "normalized" glucose tolerance; however, an OGTT after only 12 weeks would have provided very limited information regarding "diabetes prevention" and would only reflect the blood glucose–lowering effects of vildagliptin. The results from the meal tests in this study can serve, however, as the rationale for future trials testing whether prolonged administration of vildagliptin in pre-diabetic subjects would delay the diagnosis of diabetes, as has been shown for rosiglitazone (10), metformin (9), and acarbose (8).

With regard to the potential for diabetes prevention or disease modification, incretin-based therapies are considered promising because of the preclinical evidence demonstrating that GLP-1, GLP-1 receptor agonists, and DPP-4 inhibitors (11) can inhibit apoptosis and promote β-cell proliferation, thereby increasing β-cell mass. The present findings confirm that the mechanism of action of vildagliptin is fully manifest in pre-diabetic subjects, with an incidence of adverse events comparable to that with placebo and with no weight gain. A long-term diabetes prevention trial with vildagliptin appears to be justifiable, although it should be noted that there is limited clinical experience with DPP-4 inhibitors and the potential liabilities of this mechanism may become apparent with more extensive patient exposure.

In summary, in pre-diabetic subjects, a 12-week treatment with vildagliptin (50 mg q.d.) markedly increased postmeal levels of active GLP-1 and GIP, improved both α- and β-cell function, decreased postprandial hyperglycemia, and decreased A1C levels. Vildagliptin was well tolerated and weight neutral and did not cause hypoglycemia. Therefore, we conclude that vildagliptin is a good candidate that warrants further investigation to explore its full potential in pre-diabetes and would be suitable for testing in future diabetes prevention trials.

Acknowledgments— This study was funded by Novartis Pharmaceuticals Corporation.

The authors gratefully acknowledge the investigators and staff at the 28 participating sites, Bernard Reimund of Novartis for the overall management of this trial, and Beth Dunning Lower for editorial assistance and helpful discussion. A list of investigators is provided in the online appendix.

References

1. Rosenstock J, Zinman B: Dipeptidyl peptidase-4 inhibitors and the management of type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 14:98–107, 2007
2. Rosenstock J, Baron MA, Dejager S, Mills D, Schweizer A: Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Care* 30:217–223, 2007
3. Schweizer A, Couturier A, Foley JE, Dejager S: Comparison between vildagliptin and metformin to sustain reductions in HbA_{1c} over 1 year in drug-naïve patients with type 2 diabetes. *Diabet Med* 24:955–961, 2007
4. Balas B, Baig MR, Watson C, Dunning BE, Ligueros-Saylan M, Wang Y, He YL, Darland C, Holst JJ, Deacon CF, Cusi K, Mari A, Foley JE, DeFronzo RA: The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single dose administration in type 2 diabetic patients. *J Clin Endocrinol Metab* 92:1249–1255, 2007
5. Vella A, Bock G, Giesler PD, Burton DB, Serra DB, Ligueros SM, Dunning BE, Foley JE, Rizza RA, Camilleri M: effects of dipeptidyl peptidase 4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. *Diabetes* 56:1475–1480, 2007
6. El-Ouaghlidi A, Rehring E, Holst JJ, Schweizer A, Foley J, Holmes D, Nauck MA: Single doses of dipeptidyl peptidase 4 inhibitor vildagliptin do not accentuate glibenclamide induced reactive hypoglycemia but do reduce secretion of glucagon like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) in response to a glucose load in healthy subjects. *J Clin Endocrinol Metab* 92:4165–4171, 2007
7. Muscelli E, Mari A, Natali A, Astiarraga BD, Camastra S, Frascerra SD, Holst JJ, Ferrannini E: Impact of incretin hormones on β-cell function in subjects with normal or impaired glucose tolerance. *Am J Physiol* 291:E1144–E1150, 2006
8. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2: STOP-NIDDM randomised trial. *Lancet* 359: 2072–2077, 2002
9. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
10. DREAM Trial Investigators: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006
11. Baggio LL, Drucker DJ: Therapeutic approaches to preserve islet mass in type 2 diabetes. *Annu Rev Med* 57:265–281, 2006
12. Deacon CF, Nauck MA, Meier J, Hucking K, Holst JJ: Degradation of endogenous and exogenous gastric inhibitory polypeptide in healthy and in type 2 diabetic subjects as revealed using a new assay for the intact peptide. *J Clin Endocrinol Metab* 85:3575–3581, 2000
13. van Cauter E, Mestrez F, Sturis J, Polonsky KS: Estimation of insulin secretion rates from C-peptide levels: comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 41: 368–377, 1992
14. Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, Deacon CF, Holst JJ, Foley JE: Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed β-cell function in patients with type 2 diabetes. *J Clin Endocrinol Metab* 90:4888–4894, 2005
15. Ahren B, Pacini G, Foley JE, Schweizer A: Improved meal-related β-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. *Diabetes Care* 28:1936–1940, 2005
16. Scherbaum WA, Schweizer A, Mari A, Nilsson PM, Lalanne G, Jauffret S, Foley JE: Efficacy and tolerability of vildagliptin in drug-naïve patients with type 2 diabetes (T2DM) and mild hyperglycemia (Abstract). *Diabetes* 56 (Suppl. 1):A134, 2007
17. Rosenstock J, Baron MA, Camisasca RP, Cressier F, Couturier A, Dejager S: Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared to component monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab* 9:175–185, 2007
18. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ: Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care* 30: 890–893, 2007
19. Garber AJ, Schweizer A, Baron MA, Rochotte E, Dejager S: Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. *Diabetes Obes Metab* 9:166–174, 2007
20. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S: Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia* 50:1148–1155, 2007
21. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 322:15–18, 2001 .