

**Effects of the DPP-4 Inhibitor Vildagliptin on Incretin Hormones, Islet Function,
and Postprandial Glycemia in Subjects with Impaired Glucose Tolerance**

Julio Rosenstock, MD¹; James E. Foley, PhD²; Marc Rendell, MD³; Mona Landin-Olsson, MD, PhD⁴; Jens J. Holst, MD⁵; Carolyn F. Deacon, PhD⁵; Erika Rochotte, MSc⁶; Michelle A. Baron, MD²

¹Dallas Diabetes and Endocrine Center, Dallas, Texas;

²Novartis Pharmaceuticals Corporation, East Hanover, New Jersey;

³Creighton Diabetes Center, Omaha, Nebraska; ⁴University Hospital, Lund, Sweden;

⁵Panum Institute, University of Copenhagen, Denmark; ⁶Novartis Pharma AG, Basel, Switzerland

Running title: Vildagliptin in prediabetic subjects

Corresponding Author:

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

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ABSTRACT

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 qd) and placebo was conducted in 179 subjects with IGT (2-h glucose= 9.1 mmol/l, A1C= 5.9%). Plasma levels of intact GLP-1 and GIP, glucose, insulin, C-peptide, and glucagon were measured during standard meal tests performed at baseline and 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 endpoint in the total and incremental (Δ) AUC_{0-2h} for these analytes were assessed by ANCOVA; glucose AUC_{0-2h} was the primary outcome variable.

Results: Relative to placebo, vildagliptin increased GLP-1 (Δ AUC, $+6.0 \pm 1.2$ pmol/l•h, $P < 0.001$) and GIP (Δ AUC, $+46.8 \pm 5.4$ pmol/l•h, $P < 0.001$) and decreased glucagon (Δ AUC, -3.0 ± 1.0 pmol/l•h, $P = 0.003$). Although postprandial insulin levels were unaffected (Δ AUC, $+20.8 \pm 35.7$ pmol/l•h, $P = 0.561$), prandial glucose excursions were reduced (Δ AUC, -1.0 ± 0.3 mmol/l•h, $P < 0.001$), representing ~30% decrease relative to placebo. Beta-cell function as assessed by the ISR AUC_{0-2h}/glucose AUC_{0-2h} was significantly increased ($+6.4 \pm 2.0$ pmol•min⁻¹•m⁻²•mM⁻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.

This trial (NCT00237250) is registered with ClinicalTrials.gov

Vildagliptin is a potent and selective dipeptidyl peptidase-IV (DPP-4) inhibitor that improves glycemic control in patients with type 2 diabetes (T2DM) (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).

Prediabetes (ie, 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 if treatment of prediabetes with oral antidiabetic agents (OADs) can prevent the development of T2DM (8-10). Although it has been shown that metformin (9), rosiglitazone (10), and acarbose (8) can delay the diagnosis of T2DM, all of these agents have drawbacks in terms of tolerability and adverse event (AE) profile, and no agent has been found to modify the disease process.

In this regard, incretin-based therapies hold considerable promise due to the potential to increase β -cell mass suggested by preclinical studies with GLP-1, exenatide, and DPP-4 inhibitors (11). However, prior to large and long-term diabetes prevention trials, with a new oral agent such as vildagliptin, it is important to determine if DPP-4 inhibitors can enhance the incretin system and improve glucose homeostasis in a prediabetic population. Accordingly, the present 12-week, multicenter,

randomized, placebo-controlled study was undertaken to assess the tolerability and the effects of vildagliptin (50 mg qd) on incretin hormone levels, islet function, fasting and postprandial glucose control and A1C levels in subjects with IGT.

RESEARCH DESIGN AND METHODS

Study design. This was a 12-week, double-blind, randomized, placebo-controlled, parallel-group study conducted in 28 sites in the US (10), Spain (5), Finland (4), Great Britain (4), Sweden (3), and Germany (2). Each subject attended a pre-screening 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 randomized at Week 0 (Visit 3) to receive vildagliptin (50 mg qd) or placebo, and attended two additional study visits, at Week 4 and Week 12.

Study population. The study enrolled male and female subjects with IGT (FPG <7.0, 2-h post-challenge glucose \geq 7.8 but <11.1 mmol/l), aged 18 to 80 years and BMI of 23 to 45 kg/m². Females of 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: ALT or AST >3 times the upper limit of normal (ULN), direct bilirubin >1.3 times ULN, serum creatinine levels \geq 220 μ mol/l, clinically significant TSH values outside the normal

range, or fasting triglycerides >7.9 mmol/l.

Study assessments. Standard breakfast meal tests (500 kcal; 60% CHO, 30% fat, 10% protein) were performed after an overnight fast at baseline (Week 0) and Week 12 (or study endpoint). Study medication was not given prior to the meal test at baseline, but was given 15 minutes prior to the meal at Week 12. Samples for determination of active GLP-1 and GIP, glucose, insulin, C-peptide, and glucagon were obtained at times -20, 0, 15, 30, 60, 90, and 120, with the meal beginning immediately after the time 0 sample and consumed within 15 minutes. A1C was measured at Week 0 and Week 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 made at screening (Week -2), Week 0, and Week 12. All AEs were recorded and assessed as to their severity and possible relationship to 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 (SMBG) measurement <3.1 mmol/l plasma glucose equivalent.

GLP-1 was measured at Wuxi PharmaTech Co (Shanghai, China) by ELISA with N-terminally-directed antisera. GIP was measured at the Panum Institute (Copenhagen, Denmark) by RIA with an antibody (code 98171) specific for the N-terminus (12). Accordingly, the intact, biologically active forms of the incretin hormones were measured. All other laboratory assessments were made by Covance (Indianapolis, IN, USA 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 post-meal time interval. Insulin secretion relative to glucose (ISR AUC_{0-2h}/glucose AUC_{0-2h}) was calculated as a measure of β -cell function. In addition, HOMA-IR and the meal-derived insulin sensitivity index (ISI) were calculated. The primary efficacy variable was the change from baseline to endpoint (Week 12 or last available post-baseline value) in the prandial plasma glucose AUC_{0-2h}. This and all other variables were analyzed with an analysis of covariance (ANCOVA) model with treatment and pre-defined pooled center as the classification variables and baseline value as the covariate, using 2-sided tests and a statistical significance level of 0.05.

Pre-specified subanalyses of the primary outcome variable were also performed based on baseline BMI (<30 , ≥ 30 and ≥ 35 kg/m²), age group (<65 and ≥ 65 years), and gender.

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

Patients studied. Table 1 reports the baseline demographics, metabolic characteristics, and disposition of all randomized 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 approximately 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 endpoint are provided in the online appendix (Figure A1 [available at <http://care.diabetesjournals.org>]).

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 endpoint. 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 Panel A, in subjects receiving placebo, active GLP-1 increased very modestly following 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 (Appendix, Figure A2). Plasma glucagon levels were substantially suppressed during the high carbohydrate meal in subjects receiving vildagliptin relative to those receiving placebo (panel B). As shown in panel C, glucose levels increased following the meal in subjects receiving placebo and to a lesser degree in those receiving vildagliptin, and post-meal plasma insulin levels were superimposable in the two groups of subjects (panel D). However, as illustrated in the inset of Panel D, insulin secretion relative to glucose (β -cell

function) 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-hour postprandial glucose level (2-h PPG), and insulin secretion relative to glucose in subjects receiving vildagliptin or placebo. Relative to placebo, vildagliptin significantly increased the AUC_{0-2h} and ΔAUC_{0-2h} for active GLP-1 and GIP and significantly decreased both the AUC_{0-2h} and the ΔAUC_{0-2h} for glucagon and glucose. The increase in the ΔAUC s for GLP-1 and GIP represented >5-fold 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 post-meal 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 gender 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_{0-2h} were similar in non-obese (-0.9 ± 0.3 mmol/L•h), obese (-0.8 ± 0.3 mmol/L•h), and severely obese (-0.8 ± 0.5 mmol/L•h) subjects; in younger (-0.9 ± 0.3 mmol/L•h) and older (-0.7 ± 0.3 mmol/L•h) subjects; and in males ($-$

0.8±0.3 mmol/L·h) and females (-0.9±0.3 mmol/L·h).

At baseline, HOMA-IR averaged 2.6±0.2 in patients randomized to vildagliptin and 2.8±0.2 in those randomized to placebo. HOMA-IR decreased during 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 randomized to vildagliptin and 4.6±0.3 in those randomized to placebo. The ISI increased during 12-week treatment with vildagliptin (+0.5±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 endpoint. 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 non-significant trend for weight reduction in the vildagliptin treatment group.

Tolerability. One or more AE 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 AEs is provided in Table 1 of the online appendix. No specific AE occurred in more than 4 subjects in either group, and there were no notable differences in the AE profiles in subjects receiving vildagliptin or placebo. There was one

serious AE (SAE) in the vildagliptin group (congestive heart failure), and two SAEs in the placebo group (one instance of appendicitis, one instance of cellulitis). There were 3 discontinuations due to an AE in the vildagliptin group (two instances of headache, one instance of hypoesthesia), and two discontinuations due to an AE in the placebo group (one instance each of bronchospasm and eczema). There were no major changes from baseline to endpoint or between-treatment differences at endpoint 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 prediabetic population. This study clearly established that the mechanisms underlying the clinical efficacy of vildagliptin in patients with T2DM are also operant in prediabetes, as demonstrated by markedly increased postprandial incretin hormone responses - more than 5-fold and ~ 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 Δ AUC 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 prediabetes regarding incretin hormones and islet function agree

qualitatively with earlier studies performed in patients with type 2 diabetes, although quantitative comparisons are problematic due to differences in experimental design. Thus, in all studies where meal tests were performed, vildagliptin greatly increased post-meal 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 employed, treatment duration, or concomitant oral antidiabetic medication.

Vildagliptin has now been studied in a very broad spectrum of subjects, from those with prediabetes, to patients with diabetes and mild hyperglycemia (16). It also has been studied in drug-naïve patients with type 2 diabetes and moderate to severe hyperglycemia (2,3,17), as well 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, since 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 T2DM (14), the modest trends toward decreased HOMA-IR and increased ISI observed in the present study were not statistically significant when compared to placebo. This is likely 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, see Figure 1D).

OGTTs were performed initially (prior to study randomization) only to ascertain the glucose tolerance status of the study participants; this was assessed with a more physiologic 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 study endpoint 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 prediabetic 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 due to 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 prediabetic subjects, with an incidence of adverse events comparable to 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 potential liabilities of this mechanism may become apparent with more extensive patient exposure.

In summary, in prediabetic subjects, 12-week treatment with vildagliptin (50 mg qd) markedly increased post-meal 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, 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 prediabetes and would be suitable for testing in future diabetes prevention trials.

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Table 1 Baseline Demographics, Background Characteristics, and Disposition of Randomized Patients

Mean \pm SD or n (%)	Vildagliptin 50 mg qd (n = 90)	Placebo (n = 89)
Age (y)	57.1 \pm 10.7	59.8 \pm 11.5
Age <65 years	62 (68.9)	51 (57.3)
Age \geq 65 years	28 (31.1)	38 (42.7)
N (percent) male	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 (kg/m ²)	31.7 \pm 4.8	30.9 \pm 5.3
BMI <30 kg/m ²	39 (43.3)	45 (50.6)
BMI \geq 30 kg/m ²	51 (56.7)	44 (49.4)
BMI \geq 35 kg/m ²	22 (22.4)	19 (21.3)
A1C (%)	5.9 \pm 0.5	5.9 \pm 0.4
FPG (mmol/l)	6.2 \pm 0.7	6.1 \pm 0.7
2-h glucose (mmol/l) (OGTT)	9.1 \pm 0.9	9.2 \pm 0.9
Prediabetic 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

Table 2 Statistical Analysis of Meal-Test–Derived Parameters, FPG, A1C and Body Weight in the ITT Population

			Adj. Mean	Between-Group	
	n	Baseline	Change	Difference	P-value
		(Mean ± SE)	(± SE)	(Mean ± SE)	
GLP-1 AUC_{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	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 ΔAUC_{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	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_{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	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 ΔAUC_{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	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_{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	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 ΔAUC_{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	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		
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Insulin AUC _{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	74	653 ± 43	-29.4 ± 26.2	36.8 ± 37.4	0.327
Placebo	73	750 ± 52	-66.1 ± 26.8		
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Insulin ΔAUC _{0-2h} (pmol/L•h)					
Vildagliptin 50 mg qd	74	524 ± 37	-37.6 ± 25.0	20.8 ± 35.7	0.561
Placebo	73	619 ± 45	-58.4 ± 25.6		
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Glucose AUC _{0-2h} (mmol/L•h)					
Vildagliptin 50 mg qd	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		
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Glucose ΔAUC _{0-2h} (mmol/L•h)					
Vildagliptin 50 mg qd	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		
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Peak prandial glucose excursion (mmol/L)					
Vildagliptin 50 mg qd	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		
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2-hour postprandial plasma glucose level (mmol/L)					
Vildagliptin 50 mg qd	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		
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Insulin secretion relative to glucose (ISR AUC _{0-2h} /glucose AUC _{0-2h} [pmol•min ⁻¹ •m ⁻² •mM])					
Vildagliptin 50 mg qd	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		
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FPG (mmol/L)					

Vildagliptin 50 mg qd	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		
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A1C (%)					
Vildagliptin 50 mg qd	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		
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Body weight (kg)					
Vildagliptin 50 mg qd	89	87.1 ± 1.5	-0.6 ± 0.2	-0.5 ± 0.3	0.125
Placebo	89	86.9 ± 1.8	-0.1 ± 0.2		
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FIGURE LEGENDS

Figure 1: Plasma levels of active GLP-1 (Panel A), glucagon (Panel B), glucose (Panel C), and insulin (Panel D) at study endpoint during standard meal tests performed in subjects with IGT receiving vildagliptin (50 mg qd, closed triangles) or placebo (open circles). Mean \pm SE, n = 89 subjects per group (ITT population). Panel D inset shows the adjusted mean change in ISR AUC_{0-2h}/glucose AUC_{0-2h} in subjects receiving vildagliptin (closed bars) or placebo (open bars).

FIGURE 1

