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Twelve-week Monotherapy with the DPP-4 Inhibitor Vildagliptin Improves Glycemic Control in Subjects with Type 2 Diabetes

Abstract

Inhibition of dipeptidyl peptidase-4 enhances the activity of incretin hormones, improving glycemic control in subjects with type 2 diabetes. This twelve-week randomized, double-masked, placebo-controlled study assessed the efficacy and tolerability of the specific and potent oral dipeptidyl peptidase-4 inhibitor, vildagliptin (25 mg, bid, n = 70) *vs.* placebo (bid, n = 28) in previously diet-treated subjects with type 2 diabetes. Standardized meal tests were performed at baseline and endpoint. The between-group difference in adjusted mean change in HbA_{1c} from baseline to endpoint was – 0.6 ± 0.2 % (p = 0.0012) for the whole cohort (baseline 8.0 %) and – 1.2 % for subjects with baseline HbA_{1c} 8.0 – 9.5 %. Fasting glucose and mean prandial glucose were reduced by 1.1 ± 0.4 (p = 0.0043) and 1.9 ± 0.5 mmol/l (p < 0.0001), respectively. The between-group differences in corrected insulin response at peak glucose and mean prandial C-peptide were + 0.06 ± 0.02 (p = 0.0258) and + 0.10 ± 0.03 nmol/l (p = 0.0031), respectively. Vildagliptin had no effect on fasting lipid levels or body weight. The incidence of adverse events was similar in subjects receiving placebo (71.4 %) and vildagliptin (55.7 %). Conclusion: monotherapy with vildagliptin is well tolerated and improves glycemic control in diet-treated subjects with type 2 diabetes. Concomitant improvements in β-cell function were also observed. Subjects with higher baseline HbA_{1c} levels showed greater response.

Key words
Dipeptidyl peptidase IV · efficacy · glycemic control · incretin

Introduction

The incretin hormones – glucose-dependent insulinotropic polypeptide (GIP) and particularly glucagon-like peptide-1 (GLP-1) – have been reported to exert multiple metabolic effects that contribute to the regulation of glucose levels *in vivo* [1 – 3]. Strategies to enhance the activity of these incretin hormones are therefore of considerable interest as potential treatments for diabetes [4, 5]. Native GLP-1 is rapidly degraded by an enzyme known as dipeptidyl peptidase IV (DPP-4) [6, 7] and must be administered parenterally, limiting its utility as a therapeutic agent. GLP-1 agonists such as exenatide that are resistant to degradation by DPP-4 have a longer half-life [5, 7, 8]. However, as peptides, these drugs must still be administered by injection. An alternative approach to enhancing incretin activity is to prevent the inactivation of endogenously secreted incretins by inhibiting DPP-4 [5]. Several members of this new class of drugs, referred to as incretin enhancers, are in late-stage development for the treatment of type 2 diabetes.

Vildagliptin is a potent and specific inhibitor of DPP-4 [9] that increases active levels of endogenous GLP-1 and GIP [10]. It also enhances glucose-dependent insulin secretion by the pancreatic beta cell and suppresses inappropriately elevated glucagon secretion by the alpha cell [10 – 12]. Applied as a monotherapy, vildagliptin lowers mean 24 h glucose levels in subjects with type 2

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diabetes mellitus according to short-term studies [12] and has been shown to have a sustained effect on HbA_{1c} in more long-term studies when used in combination with metformin [13]. However, its effect on HbA_{1c} as a monotherapy has not yet been established. Accordingly, the aim of the present twelve-week study was to examine the efficacy and tolerability of vildagliptin (25 mg, bid) in diet-treated subjects with type 2 diabetes.

Subjects and Methods

Study design and subject characteristics

This was a randomized, double-masked, multicenter trial to compare the effects of twelve-week treatment with vildagliptin (25 mg, bid) and placebo (bid) in male and non-fertile female subjects. The study was conducted in fifteen centers in South America and Mexico. Subjects were aged at least 30 years and had a BMI between 20 and 40 kg/m^2 inclusive, type 2 diabetes that had been treated with diet only for at least eight weeks prior to enrolment, and agreed to maintain prior diet and exercise habits for the duration of the study.

Subjects with a history of type 1 or secondary forms of diabetes, significant diabetic complications, clinically significant cardiovascular abnormalities, liver disease, acromegaly, asthma, major gastrointestinal surgery, or major skin allergies were excluded from the study. Subjects with fasting triglyceride levels above 4.5 mmol/l were excluded, as were those treated with corticosteroids or sodium channel blockers within the previous three months, or any investigational drug within the previous four weeks. Subjects receiving treatment with warfarin or dicoumarin derivatives or digoxin were also excluded; subjects receiving thyroid hormone replacement could only be included if the dose had remained stable for at least three months prior to entry.

A four-week placebo run-in period preceded randomization during which the following inclusion/exclusion criteria were assessed. The mean (week – 4 and week – 2) HbA_{1c} was to lie between 6.8 and 11.0%. Subjects were excluded if fasting plasma glucose (FPG) was less than 6.1 mmol/l or more than 15 mmol/l at week – 4 or week – 2, if ALT, AST or alkaline phosphatase was more than twice the upper limit of normal (ULN), bilirubin was more than 1.3 times the ULN, hematocrit was less than 37% or serum creatinine was more than 220 µmol/l, or if TSH was abnormal. Any clinically significant laboratory abnormalities or physical exam findings precluded randomization, as did any change of body weight of more than 5% between week – 4 and week 0.

At week 0, subjects were randomized to receive vildagliptin (25 mg, bid) or placebo (bid) during the twelve-week treatment period in a ratio of 2 : 1. Fasting plasma levels of glucose and lipids were measured at weeks 1, 2, 4, 8, and 12. HbA_{1c} was measured at weeks 4, 8 and 12, and a standard meal challenge was performed at week 0 and week 12 (or endpoint). Standard biochemistry and hematology assessments were performed at every visit and urinalysis at weeks 4, 8, and 12. During the double-masked treatment period, vildagliptin or placebo was to be taken 30 minutes before breakfast and dinner.

For the meal challenge, subjects were fasted overnight and the study drug was administered 30 minutes prior to consumption of a standard 500 kcal breakfast meal that provided 62%, 31%, and 7% of calories from carbohydrate, fat, and protein, respectively. The meal was to be consumed within 15 minutes and blood samples for determination of glucose, insulin and C-peptide were obtained at 35 and 5 minutes before and at 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes after the start of the meal (designated Time 0).

All samples were analyzed at a central laboratory (Medical Research Laboratories International, Highland Heights, KY) using standardized procedures. Insulin was measured by chemiluminescence, C-peptide was measured by radioimmunoassay, glucose was measured using a hexokinase technique, and HbA_{1c} was measured using ion exchange high-performance liquid chromatography (HPLC). The normal range for this HbA_{1c} assay was 4.0 to 6.0%.

All adverse events (AEs) were recorded and assessed as to their severity and possible relationship to study medication. Subjects were provided with glucose monitoring devices and supplies and instructed on their use. An episode of hypoglycemia was defined as symptoms consistent with hypoglycemia accompanied by a glucose measurement less than or equal to 3.1 mmol/l.

Statistical analysis

The primary efficacy variable was the change from baseline (average of week – 2 and week 0) in HbA_{1c} at the end of study in the intent-to-treat (ITT) population with the last observation carried forward (LOCF). Secondary endpoints were change from baseline to endpoint in FPG, fasting insulin, fasting lipids, body weight and several parameters derived from data obtained during the standard meal challenge. These included four-hour mean insulin, glucose, and C-peptide (AUC/time) and the following indices calculated using standard formulae: HOMA-B and HOMA-R [14], insulin response corrected for peak glucose ($CIR_{[GluPeak]}$) [15] and thirty-minute insulinogenic index as well as insulin sensitivity index (ISI) [16].

Data were analyzed using an ANCOVA model including terms for treatment, baseline value, pooled center, and treatment by baseline interaction. Analyses were carried out using two-sided tests and a significance level of 0.05. Comparability of baseline characteristics was assessed by the Cochran-Mantel-Haenszel test for qualitative variables and *t*-test for quantitative variables.

Ethics and good clinical practice

Written informed consent was obtained from all participants. The protocol was approved by the Institutional Review Board/Independent Ethics Committee at each site. The study was conducted with Good Clinical Practice in accordance with the Declaration of Helsinki.

Results

Sixty-five of the 72 subjects randomized to vildagliptin (90.3%) and 26 of the 28 subjects randomized to placebo (92.9%) completed the study. Of the subjects randomized to vildagliptin, two

Table **1** Baseline characteristics of the intent-to-treat (ITT) population

Variable	*Vildagliptin 25 mg bid (n = 70)*	*Placebo bid (n = 28)*
Age (y)	56.9 ± 9.4	52.8 ± 10.0
Sex n (%)		
Male	28 (40.0)	14 (50.0)
Female	42 (60.0)	14 (50.0)
Race n (%)		
Black	2 (2.9)	0
Caucasian	33 (47.1)	13 (46.4)
Oriental	1 (1.4)	0
Other	34 (48.6)	15 (53.6)
Mean ± SD		
BMI (kg/m^2)	30.0 ± 4.5	29.9 ± 4.1
Duration of diabetes (y)	4.6 ± 5.6	3.5 ± 5.7
HbA_{1c} (%)	8.0 ± 0.9	8.1 ± 1.2
FPG (mmol/l)	9.4 ± 1.8	10.1 ± 3.2

left the study for each of the following reasons: adverse event (one reported as palpitations, one reported as gastritis), unsatisfactory therapeutic effect and withdrawal of consent; one subject was later excluded due to a protocol violation. Of the subjects randomized to placebo, one withdrew consent and one did not complete the study due to administrative problems. Table **1** reports the baseline demographic and metabolic characteristics of the ITT population. There was a higher percentage of females in the active treatment group than in the placebo group, and the mean age of subjects randomized to vildagliptin was somewhat higher than that of subjects randomized to placebo.

Fig. **1** shows the time-course of HbA_{1c} (Panel **a**) and fasting plasma glucose (FPG, Panel **b**) during twelve-week treatment with vildagliptin or placebo, and shows that HbA_{1c} decreased steadily in subjects receiving vildagliptin, but remained unchanged over twelve weeks in placebo-treated subjects. The adjusted mean change in HbA_{1c} from baseline (8.0%) to endpoint was – 0.6 ± 0.1 % in subjects receiving vildagliptin and 0.0 ± 0.2 % in subjects receiving placebo (between-group difference: – 0.6 ± 0.2 %, p = 0.0012). As illustrated in Fig. **1 b**, FPG also decreased steadily in subjects receiving vildagliptin (adjusted mean Δ FPG from baseline to endpoint = – 0.9 ± 0.2 mmol/l) but showed no relevant change in placebo-treated subjects (adjusted mean Δ FPG = + 0.2 ± 0.3 mmol/l). The between-group difference was – 1.1 ± 0.4 mmol/l (p = 0.0043).

A pre-specified subgroup analysis was performed to examine the effect of baseline HbA_{1c} on the clinical response. As shown in Fig. **2**, in vildagliptin-treated subjects with a higher baseline HbA_{1c} (8.0% < HbA_{1c} ≤ 9.5%, mean: 8.5%); mean Δ HbA_{1c} (– 1.0 ± 0.2%) was twice that in vildagliptin-treated subjects with a lower baseline HbA_{1c} (7.0% ≤ HbA_{1c} ≤ 8.0%, mean = 7.5%, Δ= – 0.5 ± 0.1%). HbA_{1c} increased modestly and to a similar degree in placebo-treated subjects with lower baseline (+ 0.1 ± 0.3%) and higher baseline (+ 0.2 ± 0.2%), thus the between-group difference was greater in subjects with higher baseline HbA_{1c} (– 1.2%) *vs.* lower baseline HbA_{1c} (– 0.7%).

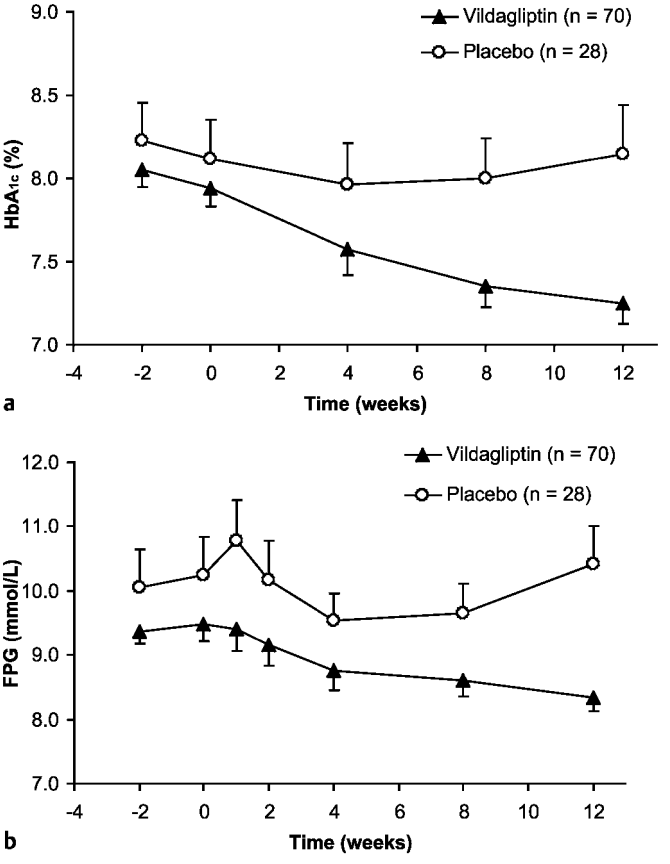

Fig. **1** Mean ± SE HbA_{1c} (Panel **a**) and fasting plasma glucose (FPG, Panel **b**) in the ITT population. Open circles, placebo; closed triangles, vildagliptin.

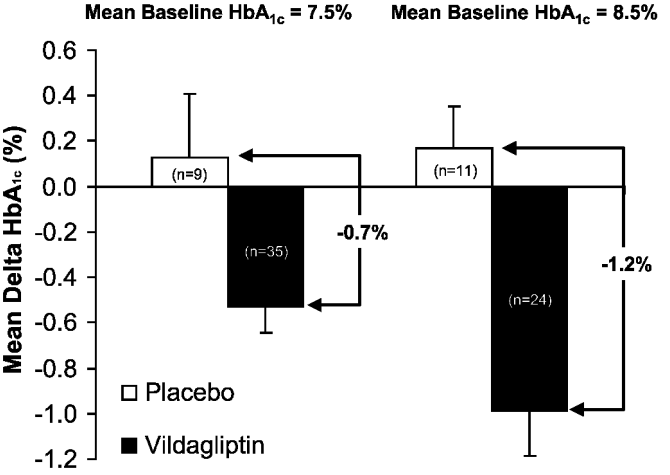

Fig. **2** Mean ± SE change in HbA_{1c} from baseline to week 12 or endpoint in subgroups of subjects with low (≥ 7.0%, ≤ 8.0%) and high (≥ 8.0%, ≤ 9.5%) baseline HbA_{1c} together with the between-group difference. Number of subjects in each subgroup is indicated within the bars.

Fig. **3** depicts the glucose and insulin profiles during standard meal tests performed at baseline and endpoint in subjects randomized to receive vildagliptin (Panels **a** and **b**) or placebo (Panels **c** and **d**). As illustrated in Fig. **3 a**, vildagliptin decreased post-meal glucose levels throughout the meal test. The adjusted mean change from baseline to endpoint 4 h mean prandial glucose was – 1.7 ± 0.3 mmol/l in vildagliptin-treated subjects. In

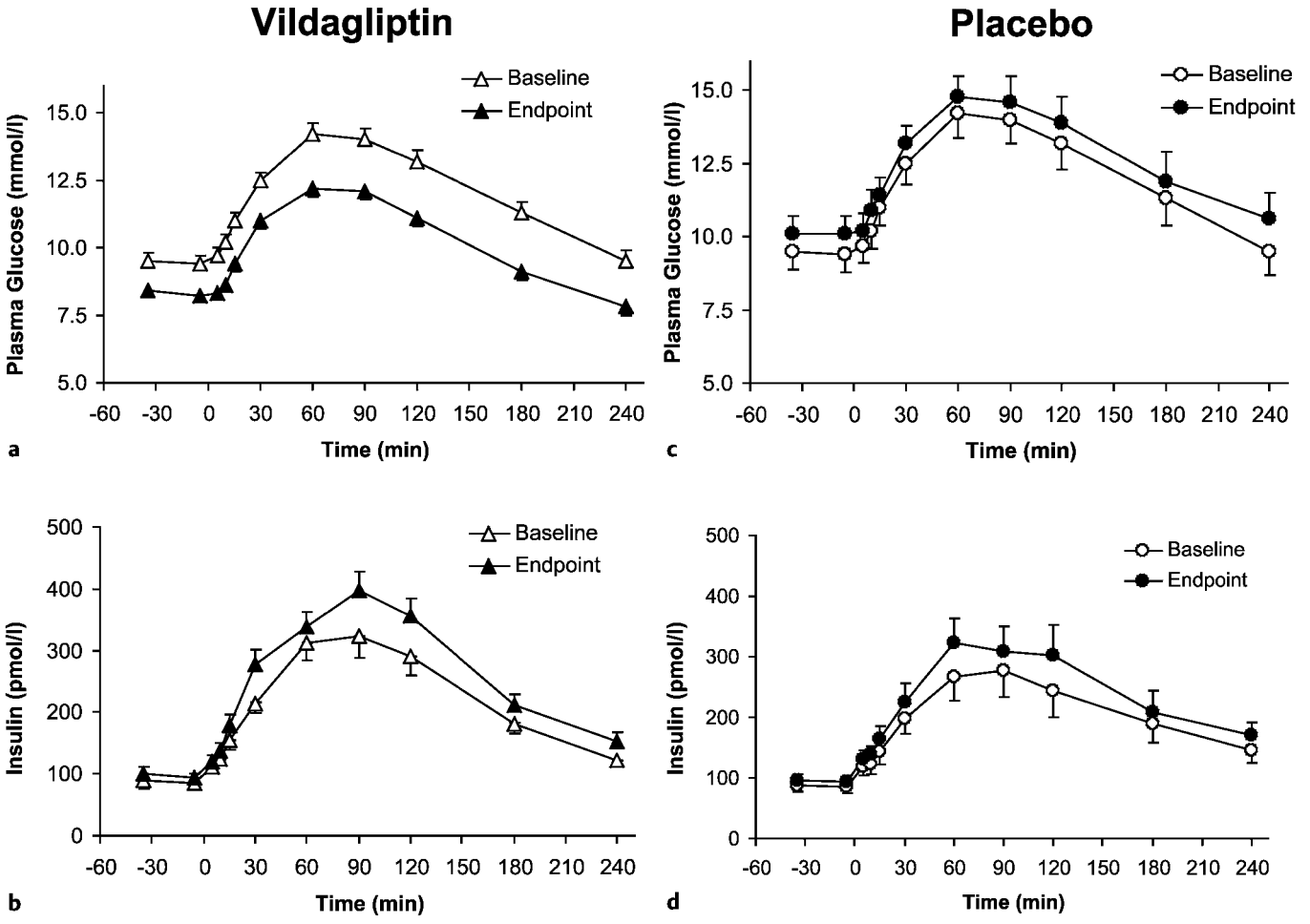

Fig. **3** Plasma glucose (Panels **a, c**) and insulin (Panels **b, d**) during standardized meal challenge performed at baseline (open symbols) and week 12 or endpoint (closed symbols) in subjects receiving vildagliptin (25 mg, bid, n = 70, triangles) or placebo (n = 28, circles). Mean ± SE, ITT population.

contrast, in placebo-treated subjects glucose levels during meal tests tended to be higher at endpoint than at baseline (adjusted mean change from baseline to endpoint in 4 h mean prandial glucose = + 0.2 ± 0.4 mmol/l. The between-group difference was – 1.9 ± 0.5 mmol/l ($p < 0.0001$). As shown in Fig. **3 b** und **d**, although prandial insulin levels tended to be higher at endpoint than at baseline in vildagliptin-treated subjects, they also tended to be higher at endpoint than at baseline in placebo-treated subjects. Thus, there was no significant difference between groups in prandial insulin levels.

Indices of insulin secretion and action were calculated from data obtained during the standard meal tests and are reported in Table **2**. Of these six parameters, only the 4 h mean C-peptide level, glucose level and corrected insulin response at peak glucose ($CIR_{[GluPeak]}$) were significantly affected by vildagliptin.

There was no statistically significant effect of vildagliptin on any lipid parameter. Similarly, the between-group difference in the adjusted mean change from baseline to endpoint in body weight (+ 0.5 ± 0.5 kg) was not statistically significant.

Safety and tolerability

In general, vildagliptin appeared to be well-tolerated. A total of 39 of 70 subjects (55.7%) treated with vildagliptin experienced at least one AE, whereas 20 of 28 placebo-treated subjects (71.4%) experienced one or more AEs. All reported AEs were classified by the investigator as being mild or moderate in severity, with most of the events in either treatment group (~ 80% of the events) classified as mild. Table **3** reports the number and percentage of subjects experiencing any specific AE that occurred in at least 5% of subjects in either group, and specifies the number and percentage of subjects experiencing one or more event suspected by the investigator to be related to study drug. Dizziness, headache, increased blood pressure (classified as hypertension whether or not blood pressure exceeded diagnostic criteria), and increased sweating were the most prevalent AEs in the subjects receiving vildagliptin, and chest pain was the most prevalent AE reported by subjects receiving placebo. In fewer than 5% of subjects experiencing any specific AE, the event was suspected to be related to the study drug. One episode of hypoglycemia (plasma glucose less than or equal to 3.1 mmol/l) occurred in a subject receiving vildagliptin; this was attributed to a delayed meal. One vildagliptin-treated subject reported mild nausea and one placebo-treated subject reported moderate nausea. There were no serious AEs and no deaths during the double-masked treatment period.

Table **2** Adjusted mean change from baseline to endpoint and between-group difference in indices of insulin secretion[a] and action[b]

	Vildagliptin Mean ± SEM	*n*	*Placebo Mean ± SEM*	*n*	*Difference*	*p-value*
[a]Insulinogenic Index	0.18 ± 0.07	65	– 0.06 ± 0.11	25	0.24 ± 0.13	0.0674
[a]$CIR_{[GluPeak]}$	0.8 ± 0.01	64	0.02 ± 0.02	25	0.06 ± 0.02	**0.0258**
[a]4 hmean insulin	44.1 ± 12.4	64	27.8 ± 19.2	25	16.3 ± 22.4	0.4680
[a]4 hmean C-peptide	0.07 ± 0.02	63	– 0.03 ± 0.03	24	0.10 ± 0.03	**0.0031**
[a]HOMA-B	11.0 ± 3.5	66	0.8 ± 5.5	25	10.2 ± 6.3	0.1127
[b]HOMA-R	0.02 ± 0.41	66	0.27 ± 0.65	25	– 0.24 ± 0.75	0.7469
[b]ISI	0.15 ± 0.33	64	– 0.09 ± 0.51	25	0.25 ± 0.59	0.6794
[b]4 h mean glucose	– 1.7 ± 0.25	63	0.20 ± 0.38	26	– 1.91 ± 0.46	**< 0.0001**

Table **3** Adverse events occurring in at least 5% of either treatment group

Adverse Event	*Vildagliptin 25 mg bid (n = 70)*		*Placebo (n = 28)*	
Any adverse event	39 (55.7)		20 (71.4)	
	Total n (%)	Suspected[a] n (%)	Total n (%)	Suspected[a] n (%)
Dizziness	6 (8.6)	2 (2.9)	0	0
Headache	5 (7.1)	1 (1.4)	1 (3.6)	0
Hypertension	4 (5.7)	0	1 (3.6)	0
Increased sweating	4 (5.7)	3 (4.3)	1 (3.6)	1 (3.6)
Abdominal pain	3 (4.3)	2 (2.9)	2 (7.1)	1 (3.6)
Anxiety	1 (1.4)	0	2 (7.1)	0
Chest pain	1 (1.4)	0	3 (10.7)	0
Dyslipidemia	1 (1.4)	0	2 (7.1)	0
Fatigue	0	0	2 (7.1)	0

[a] Number and percentage of subjects with a specific adverse event suspected by investigator to be related to study drug.

Discussion

The present findings are the first to describe the efficacy of monotherapy with the DPP-4 inhibitor vildagliptin on HbA_{1c} in subjects with type 2 diabetes. At a dose of 25 mg bid, vildagliptin decreased HbA_{1c} by 0.6% relative to placebo in the study population as a whole after twelve weeks of treatment. The magnitude of the reduction in HbA_{1c} was dependent on the baseline level with greater reductions (1.2 ± 0.2% *vs.* placebo) in a subset of subjects with a high baseline HbA_{1c} (8.0% to 9.5%, mean = 8.5%), indicating that vildagliptin retains its effectiveness over a wide range of disease severity.

The changes in both FPG (– 1.1 mmol/l relative to placebo) and mean prandial glucose level (– 1.9 mmol/l relative to placebo) observed in the present study are similar to those reported in a four-week study on monotherapy with a 100 mg qd dose regimen in drug-naïve subjects with type 2 diabetes (– 0.7 and – 1.5 mmol/l, respectively). Further, the between-group difference in HbA_{1c} at week 4 in the current study (– 0.4%) was similar to that in the earlier study [12].

Our results are also similar to those of a twelve-week add-on study on vildagliptin administered as 50 mg qd or placebo in patients treated with a stable dose of metformin [13]. In that study, the change from baseline to week 12 (difference from placebo) of HbA_{1c}, FPG and mean post-meal glucose averaged – 0.6%, – 1.2 mmol/l and – 2.2 mmol/l, respectively. Thus with regard to dosing regimen, 25 mg bid and 50 mg qd appeared to exert similar effects. Further, the reduction in HbA_{1c} after twelve weeks in the add-on to metformin study was largely maintained after twelve months, whereas HbA_{1c} continued to increase during the study extension in subjects maintaining a stable metformin dosage without additional therapy. Since in our study the magnitude of the decrease in HbA_{1c} was similar in the first twelve weeks, it will be interesting to see whether longer-term studies with vildagliptin monotherapy confirm this apparent durability of effect.

Although the mechanisms by which vildagliptin improves glycemic control were not directly addressed in the present study, prior studies have demonstrated that vildagliptin potently inhibits DPP-4, increases active GLP-1 levels and suppresses glucagon [12]. The observation that insulin levels were not significantly altered by vildagliptin in a setting where glucose levels were reduced is consistent with enhanced beta cell function. The significant increases relative to placebo in 4 h mean post-meal C-peptide levels and in the $CIR_{[GluPeak]}$ are also consistent with improved beta cell function. Similar results were also seen in both the four-week monotherapy study and the twelve-week add-on to metformin study [12,13]. Improved beta cell function with vildagliptin has also been demonstrated using mathematical models of beta cell function, both when used as a monotherapy [10] and in combination with metformin [11]. Since improved glycemic control *per se* may lead to improvements in insulin secretion, a long-term, actively controlled study would be necessary to demonstrate conclusively that vildagliptin enhances beta-cell function. Nevertheless, the observation that improvements in insulin secretion are sustained for up to fifty-two weeks in vildagliptin-treated subjects support the hypothesis of a direct benefit on beta cells [11].

In the present study, as in previous small studies with vildagliptin [10,12,13] or another DPP-4 inhibitor [17], vildagliptin appeared to be well-tolerated. The most common adverse events in vildagliptin-treated subjects were mild or moderate, and few were suspected to be drug-related. Suspected drug-related AEs in subjects receiving vildagliptin were largely symptoms consis-

tent with low blood glucose, although only one episode of hypoglycemia occurred in a vildagliptin-treated subject, which was thought to be precipitated by a delayed meal. Nausea occurred in one subject randomized to vildagliptin (1.4%) and one placebo-treated subject (3.6%). Although larger and longer trials with both monotherapy and in combination with other oral antidiabetic agents will be necessary to establish the safety and tolerability profile of vildagliptin, the present data suggest that nausea/vomiting would not be a dose-limiting side effect of DPP-4 inhibition.

In summary, twelve-week monotherapy with the incretin-enhancer vildagliptin (25 mg, bid) reduced fasting and postprandial glucose levels by 1.1 and 1.9 mmol/l relative to placebo, respectively, and decreased HbA_{1c} by 0.6%. These findings are similar to those with the same total daily dose administered once daily in subjects who had not responded adequately to metformin. The mean reduction in HbA_{1c} was 1.2% relative to placebo in subjects with baseline HbA_{1c} of more than 8.0% but at most 9.5%. In addition, data from a standard meal test indicated improved beta-cell function. The incidence of any AE was higher in placebo-treated subjects (71.4%) than in vildagliptin-treated subjects (55.7%), most AEs were classified as mild and few adverse events were suspected to be drug-related. We conclude that monotherapy with the DPP-4 inhibitor vildagliptin is efficacious and well-tolerated in subjects with type 2 diabetes.

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