Management of Type 2 Diabetes in Treatment-Naive Elderly Patients

Benefits and risks of vildagliptin monotherapy

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OBJECTIVE — The purpose of this study was to evaluate the efficacy and safety of vildagliptin in elderly patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Efficacy data from five double-blind, randomized, placebo- or active-controlled trials of ≥24 weeks' duration were pooled. Effects of 24-week vildagliptin monotherapy (100 mg daily) were compared in younger (<65 years, n = 1,231) and older (≥65 years, n = 238) patients. Safety data from eight controlled clinical trials of ≥12-weeks' duration were pooled; adverse event profiles in younger (n = 1,890) and older (n = 374) patients were compared.

RESULTS — Mean baseline A1C and fasting plasma glucose (FPG) were significantly lower in older (70 years: 8.3 ± 0.1% and 9.6 ± 0.1 mmol/l, respectively) than in younger (50 years: 8.7 ± 0.0% and 10.5 ± 0.1 mmol/l, respectively) patients. Despite this, the adjusted mean change from baseline (AMΔ) in A1C was −1.2 ± 0.1% in older and −1.0 ± 0.0% in younger vildagliptin-treated patients (P = 0.092), and the AMΔ in FPG was significantly larger in older (−1.5 ± 0.2 mmol/l) than in younger (−1.1 ± 0.1 mmol/l, P = 0.035) patients. Body weight was significantly lower at baseline in older (83.4 ± 1.0 kg) than in younger (92.0 ± 0.6 kg) patients. Weight decreased significantly in the older subgroup (AMΔ −0.9 ± 0.3 kg, P = 0.007), whereas smaller, nonsignificant decreases occurred in younger patients (AMΔ −0.2 ± 0.1 kg). Adverse event rates were slightly higher in older than in younger subgroups but were lower among older, vildagliptin-treated subjects (63.6%) than in the pooled active comparator group (68.1%). Vildagliptin treatment did not increase adverse events among older patients with mild renal impairment (62.0%). Hypoglycemia was rare (0.8%) in the elderly patients, and no severe events occurred.

CONCLUSIONS — Vildagliptin monotherapy was effective and well tolerated in treatment-naive elderly patients.

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Abbreviations: AMΔ, adjusted mean change; DPP-4, dipeptidyl peptidase IV; FPG, fasting plasma glucose; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; OAD, oral antidiabetic drug; SAE, serious adverse event.

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

Type 2 diabetes is among the most common chronic conditions in older adults. Nearly 20% of individuals aged ≥65 years are affected, although in nearly half of them diabetes is undiagnosed (1). Management of type 2 diabetes in elderly individuals can be particularly challenging for a number of reasons (2). First, hypoglycemia is more common in older than in younger people taking oral antidiabetic drugs (OADs), is often more severe, and can precipitate serious events such as falls and hip fractures. This higher incidence is due in part to higher rates of conditions such as depression, cognitive dysfunction, poor appetite, and irregular eating habits that predispose to hypoglycemia. Age-associated abnormalities in counterregulation (3) can also impair the patient's ability to recognize and respond to hypoglycemia. Second, elderly patients with type 2 diabetes have a high prevalence of comorbidities (4) and, accordingly, concomitant use of multiple medications is very common. Further, undiagnosed renal impairment may be present in >50% of elderly patients with type 2 diabetes (4). These issues may limit therapeutic choices and can lead to inappropriate, less aggressive treatment goals. Thus, fewer than half of patients aged ≥65 years achieve recommended levels of glycemic control (A1C <7.0%) (5). Collectively, these data highlight a substantial unmet medical need for safe and effective therapeutic agents for elderly patients with type 2 diabetes.

Vildagliptin is a potent and selective dipeptidyl peptidase IV (DPP-4) inhibitor that improves glycemic control in patients with type 2 diabetes through incretin-hormone–mediated increases in both α- and β-cell responsiveness to glucose (6). In studies enrolling OAD-naive patients with type 2 diabetes, 24 weeks' treatment with vildagliptin monotherapy (50 or 100 mg daily) was reported to decrease A1C by 0.9–1.1% (7,8).

Because the effects of incretin hormones to increase insulin secretion (9) and of glucagon-like peptide-1 (GLP-1) to suppress glucagon secretion (10) are

glucose dependent, DPP-4 inhibitors such as vildagliptin are associated with a very low risk of hypoglycemia. Further, experience thus far with vildagliptin indicates that it is well tolerated, as demonstrated in placebo-controlled (7,11) and active-controlled studies with metformin (12) and thiazolidinediones (8,13). Hence, vildagliptin appears to possess many characteristics that could make it a useful therapeutic option for treatment of type 2 diabetes in elderly individuals.

The purpose of the present analysis was to ascertain the efficacy and tolerability of vildagliptin monotherapy in elderly patients with type 2 diabetes. Thus, data from vildagliptin monotherapy trials were pooled, and the efficacy and safety of vildagliptin in patients aged ≥65 years were compared with those in patients <65 years of age.

RESEARCH DESIGN AND METHODS

— Studies were multicenter, randomized, double-blind, parallel-group, placebo- or active-controlled trials of 12–52 weeks' duration, with one or more vildagliptin monotherapy arms. Twenty-four-week efficacy data from all completed trials of ≥24 weeks' duration were pooled (patients receiving 100 mg vildagliptin daily as monotherapy, either 50 mg b.i.d. or 100 mg q.d.) from two placebo-controlled and three active-controlled studies (n = 1,469). To provide the most comprehensive information available, safety data from all completed trials of ≥12 weeks' duration (i.e., the aforementioned five trials, two placebo-controlled 12-week studies, and one active-controlled 12-week study) were pooled from patients receiving 50 mg q.d., 50 mg b.i.d., or 100 mg q.d. vildagliptin (n = 2,264), all active comparators (up to 1,000 mg b.i.d. metformin, 30 mg q.d. pioglitazone, or 8 mg q.d. rosiglitazone, n = 735), and placebo (n = 347). Details about study designs and inclusion and exclusion criteria are summarized in Table A1 of the online appendix (available at http://dx.doi.org/10.2337/dc07-1188) and are also provided in the individual study publications (7,8,11–13).

Study assessments

A1C, fasting plasma glucose (FPG), body weight, fasting lipid levels (triglycerides and total, LDL, HDL, non-HDL, and VLDL cholesterol), and sitting systolic and diastolic blood pressure were measured periodically, and the changes from baseline to week 24 are reported as efficacy parameters. Changes in A1C were also assessed in the prespecified subgroups of patients with lower (≤8.0 or ≤9.0%) and higher (>8.0 or >9.0%) baseline A1C levels and of patients with lower (<30 or <35 kg/m^2) and higher (≥30 or ≥35 kg/m^2) baseline BMI. Changes in body weight were assessed in the same BMI subgroups. In addition, responder analyses were performed to determine the percentage of patients achieving A1C <7.0% in the overall population and in the prespecified subgroups of patients with a baseline A1C ≤8%.

Glomerular filtration rate (GFR) was estimated with the Modification of Diet in Renal Disease study method (14), and patients were classified according to criteria previously specified in guidelines published by the Food and Drug Administrations into a group with normal renal function (GFR >80 ml/min × 1.73/m^2) and a group with mild renal impairment (GFR ≤80 and >50 ml/min × 1.73/m^2). All adverse events were recorded and assessed by the investigator as to the severity and possible relationship to the study medication. 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-monitoring of blood glucose measurement of <3.1 mmol/l plasma glucose equivalent. Severe hypoglycemia was defined as any episode requiring the assistance of another party.

All laboratory assessments were performed by central laboratories: Bioanalytical Research Corporation-US (Lake Success, NY), Bioanalytical Research Corporation-EU (Ghent, Belgium), Diabetes Diagnostics Laboratory (Columbia, MO), Covance-US (Indianapolis, IN), or Medical Research Laboratories International (Zaventem, Belgium). A1C was measured by high-performance liquid chromatography (ion exchange or boronate affinity). All laboratories were either National Glycohemoglobin Standardization Program certified or National Glycohemoglobin Standardization Program network laboratories, thus allowing traceability to the Diabetes Control and Complications Trial reference method of A1C measurement.

Data analysis

The safety population comprised all patients receiving vildagliptin monotherapy (50 or 100 mg daily) for whom at least one postbaseline safety assessment was available. The efficacy population comprised all patients receiving vildagliptin (100 mg daily: 50 mg b.i.d. or 100 mg q.d.) for whom both a baseline and postbaseline efficacy assessment were available. Changes from baseline in efficacy parameters were analyzed using an ANCOVA model containing treatment, study, age-group, treatment × age-group interaction, and baseline value as a covariate. Within-group comparisons (end point versus baseline) and between-group comparisons (patients aged ≥65 years vs. patients aged <65 years) were made using two-sided tests at a significance level of 0.05. Safety data are summarized for the overall safety population and for the younger and older subgroups; statistical comparisons of safety data were not made.

Ethics and good clinical practice

All participants provided written informed consent. All protocols were approved by the independent ethics committee/institutional review board at each study site. All studies were conducted using good clinical practice and in accordance with the Declaration of Helsinki.

RESULTS

— Table A2 of the online appendix summarizes the baseline anthropometric and disease characteristics of the overall population and of the younger (mean age ~50 years) and older (mean age ~70 years) subgroups of patients in the safety population. Patients aged ≥65 years represented ~17% of the pooled safety database. The majority of all patients were Caucasian and obese, with mean A1C of 8.6% and mean FPG of 10.1 mmol/l. Minorities represented a larger proportion of the younger subgroup, whereas the older subgroup was on average less obese (with only about half the prevalence of severe obesity than the younger subgroup) and had better glycemic control while receiving no OAD, despite a somewhat longer mean disease duration. More than 85% of the older subgroup had one or more additional cardiovascular risk factors (vs. ~62% of the younger subgroup), and nearly two-thirds of the older patients had undiagnosed mild renal impairment (vs. ~28% of the younger subgroup). More than 75% of the older subgroup had hypertension, about half had dyslipidemia, and nearly 25% had coronary artery disease, whereas these conditions were, as expected, much less prevalent in the younger subgroup. Furthermore, the elderly patients were taking an average of 9.8 concomitant medications at study en-

Table 1—*Efficacy parameters in patients receiving vildagliptin (100 mg daily)*

	All		Aged <65 years		Aged ≥65 years	
	BL	AMΔ	BL	AMΔ	BL	AMΔ
n	1,469		1,231		238	
A1C (%)	8.6 ± 0.0	−1.0 ± 0.0*	8.7 ± 0.0	−1.0 ± 0.0*	8.3 ± 0.1†	−1.2 ± 0.1*
FPG (mmol/l)	10.4 ± 0.1	−1.1 ± 0.1*	10.5 ± 0.1	−1.1 ± 0.1*	9.6 ± 0.1†	−1.5 ± 0.2*†
Body weight (kg)	90.6 ± 0.5	−0.3 ± 0.1	92.0 ± 0.6	−0.2 ± 0.1	83.4 ± 1.0†	−0.9 ± 0.3*
Responder analyses (achieving A1C <7.0%)	*n*‡	*n* (%) responders	*n*‡	n (%) responders	n‡	*n* (%) responders
Overall	1,462	548 (37.5)	1,226	438 (35.7)	236	110 (44.6)†
Baseline A1C ≤8.0%	526	286 (54.4)	405	210 (51.9)	121	76 (62.8)†
Fasting lipids (mmol/l)		AM%Δ		AM%Δ		AM%Δ
Triglycerides	2.4 ± 0.1	−3.3 ± 1.3*	2.4 ± 0.1	−2.8 ± 1.4*	2.1 ± 0.1	−6.3 ± 2.9*
Total cholesterol	5.3 ± 0.0	−2.2 ± 0.4*	5.3 ± 0.0	−2.0 ± 0.5*	5.3 ± 0.1	−3.0 ± 1.0*
LDL	3.1 ± 0.0	−0.7 ± 0.8	3.1 ± 0.0	−0.3 ± 0.8	3.1 ± 0.1	−2.5 ± 1.7
HDL	1.2 ± 0.0	4.5 ± 0.6*	1.1 ± 0.0	4.5 ± 0.6*	1.3 ± 0.0	4.8 ± 1.3*
Non-HDL	4.1 ± 0.0	−3.3 ± 0.6*	4.2 ± 0.0	−3.0 ± 0.6*	4.0 ± 0.1	−4.9 ± 1.3*
VLDL	0.95 ± 0.01	−3.4 ± 1.1*	1.0 ± 0.0	−3.0 ± 1.3*	0.9 ± 0.0	−5.3 ± 2.4*
Blood pressure (mmHg)		mean Δ		mean Δ		mean Δ
Diastolic	81.3 ± 0.3	−1.4 ± 0.2*	81.5 ± 0.2	−1.3 ± 0.2*	80.1 ± 0.5	−2.0 ± 0.5*
Systolic	132.1 ± 0.3	−2.2 ± 0.3*	130.8 ± 0.4	−2.2 ± 0.4*	138.5 ± 0.8	−2.2 ± 1.0*
Subgroup analyses	BL (*n*)	AMΔ	BL (*n*)	AMΔ	BL (*n*)	AMΔ
A1C (%)						
BL A1C ≤8.0%	7.6 (533)	−0.6 ± 0.0*	7.6 (410)	−0.6 ± 0.1*	7.6 (123)	−0.7 ± 0.1*
BL A1C >8.0%	9.2 (936)	−1.3 ± 0.1*	9.2 (821)	−1.2 ± 0.1*	9.0 (115)	−1.4 ± 0.1*
BL A1C ≤9.0%	8.1 (995)	−0.8 ± 0.0*	8.1 (806)	−0.7 ± 0.0*	7.9 (189)	−0.9 ± 0.1*
BL A1C >9.0%	9.9 (474)	−1.6 ± 0.1*	9.9 (425)	−1.6 ± 0.1*	9.7 (49)	−1.7 ± 0.2*
BL BMI <30 kg/m^2	8.7 (613)	−1.2 ± 0.1*	8.8 (487)	−1.2 ± 0.1*	8.4 (126)	−1.3 ± 0.1*
BL BMI ≥30 kg/m^2	8.6 (855)	−0.9 ± 0.1*	8.7 (743)	−0.9 ± 0.1*	8.2 (112)	−1.0 ± 0.1*
BL BMI <35 kg/m^2	8.7 (1,034)	−1.1 ± 0.0*	8.8 (838)	−1.1 ± 0.1*	8.3 (196)	−1.2 ± 0.1*
BL BMI ≥35 kg/m^2	8.6 (434)	−0.9 ± 0.1*	8.6 (392)	−0.9 ± 0.1*	8.2 (42)	−0.9 ± 0.2*
Body weight (kg)						
BL BMI <30 kg/m^2	75.6 (613)	−0.0 ± 0.1	75.8 (487)	0.1 ± 0.1	74.5 (126)	−0.5 ± 0.3†
BL BMI ≥30 kg/m^2	101.3 (855)	−0.6 ± 0.2*	102.6 (743)	−0.5 ± 0.2*	93.3 (112)	−1.3 ± 0.4*†
BL BMI <35 kg/m^2	82.1 (1,034)	−0.2 ± 0.1	82.8 (838)	−0.1 ± 0.1	79.4 (196)	−0.8 ± 0.2*†
BL BMI ≥35 kg/m^2	110.7 (434)	−0.6 ± 0.3*	111.7 (392)	−0.6 ± 0.3*	101.8 (42)	−1.4 ± 0.7*

Data are means ± SE unless otherwise indicated. *$P < 0.05$ vs. baseline (within group); †$P < 0.05$ vs. younger subgroup. ‡Patients with both baseline A1C ≥7% and an end point value. BL, baseline.

rollment compared with 4.4 in the younger subgroup, so twice as many elderly patients were taking ≥5 concomitant medications as their younger counterparts. The baseline characteristics of patients in the efficacy population were similar to those of patients in the safety population.

Efficacy

Table 1 summarizes all efficacy parameters, responder analyses, and subgroup analyses of A1C and body weight in the overall efficacy population and in the younger and older subgroups. In the overall population, vildagliptin significantly decreased A1C by 1.0% from a mean baseline of 8.6%. The decrease in the elderly subgroup (adjusted mean change [AMΔ] −1.2%) tended to be greater ($P = 0.092$) than that in the younger subgroup (AMΔ −1.0%) despite having a significantly lower baseline A1C (8.3 vs. 8.7%). Because the majority of the available data derived from active-controlled trials, there were only 26 elderly patients receiving placebo. Baseline A1C was 8.2 ± 0.2% in these patients with AMΔ of −0.5 ± 0.3%, and a similar reduction (0.3 ± 0.1%) was also seen in the younger subgroup ($n = 156$), driven primarily by a single study (11).

For FPG, the difference between older and younger vildagliptin-treated patients achieved statistical significance. In the older subgroup, vildagliptin decreased FPG by a significantly greater degree (AMΔ −1.5 mmol/l, $P = 0.035$) from a significantly lower baseline value (9.6 vs. 10.5 mmol/l).

In the elderly subgroup, 47% of the patients achieved the American Diabetes Association recommended target A1C (<7.0%) versus 36% of the younger subgroup ($P = 0.002$ for younger versus older). In patients with baseline A1C ≤8.0% (mean of 7.6% in both subgroups), the percentage of patients achieving the target was also significantly greater for the elderly (63%) than for the younger patients (52%, $P = 0.034$ younger versus older).

Vildagliptin did not significantly affect body weight relative to baseline in the

overall population (AMΔ −0.3 kg) or in the younger subgroup (AMΔ −0.2 kg). In contrast, in older patients, vildagliptin significantly decreased body weight (AMΔ −0.9 kg) from a baseline (83.4 kg) that was significantly lower than that in younger patients (92.0 kg). In both the younger and the older subgroups, weight loss was more substantial in the more obese patients (Table 1).

In the overall efficacy population as well as in both subgroups, vildagliptin produced modest but statistically significant improvements in the fasting lipid profile. Although there were no significant differences between the responses observed by age-groups, the most substantial changes were observed in the elderly subgroup. Very modest reductions in blood pressure were seen in the overall population, and these did not differ between older and younger subgroups (Table 1).

Subgroup analyses

Both baseline A1C and baseline BMI appeared to influence the magnitude of the responses to vildagliptin, and the efficacy of vildagliptin was consistently of slightly greater magnitude in elderly patients compared with younger patients across all prespecified subgroups (Table 1). Although reductions in A1C were somewhat larger in the leaner subgroups, the enhanced efficacy of vildagliptin in older versus younger patients was not explained by their lesser degree of obesity. Thus, when analyses of covariance were performed to adjust for baseline BMI, the same differential effect remained for both A1C (between-group difference in AMΔ −0.13 ± 0.09%, $P = 0.140$) and FPG (between-group difference in AMΔ −0.4 ± 0.2 mmol/l, $P = 0.041$).

Safety and tolerability

Figure 1 depicts adverse event profiles in the overall safety population (Fig. 1*A*) and in the younger (Fig. 1*B*) and older (Fig. 1*C*) subgroups. Adverse events were slightly more frequent in older (63.6%) than in younger (60.6%) patients receiving vildagliptin, but a more substantial difference was seen for the pooled active comparator group (68.1% in the elderly subgroup vs. 63.0% in the younger subgroup). Further, no excess of adverse events in elderly versus younger patients with mild renal impairment receiving vildagliptin (62.0 vs. 62.1%) and no excess in older patients with mild renal impairment compared with older patients with normal renal function (62.0 vs. 64.3%) were noted, whereas the adverse event rate in renally impaired patients receiving an active comparator was higher for both older (74.6%) and younger (71.7%) patients. Adverse events suspected to be drug related were more common in both older (18.1%) and younger (17.9%) patients receiving an active comparator than in older (12.3%) or younger (9.2%) patients receiving vildagliptin. Serious adverse events (SAEs) were reported by a somewhat higher percentage of older (6.4%) than of younger (3.1%) vildagliptin-treated patients or of older patients receiving an active comparator (2.6%); this represented a total of 24 patients with SAEs, distributed across 13 "primary system organ classes" (Medical Dictionary for Regulatory Affairs categories), with no cluster of events within any specific preferred term. None of the SAEs in vildagliptin-treated elderly patients was suspected to be drug related. A possible drug-related SAE was reported by one patient receiving vildagliptin in the younger subgroup and by one elderly patient receiving an active comparator. Discontinuations due to an adverse event were slightly more frequent in older (3.7%)

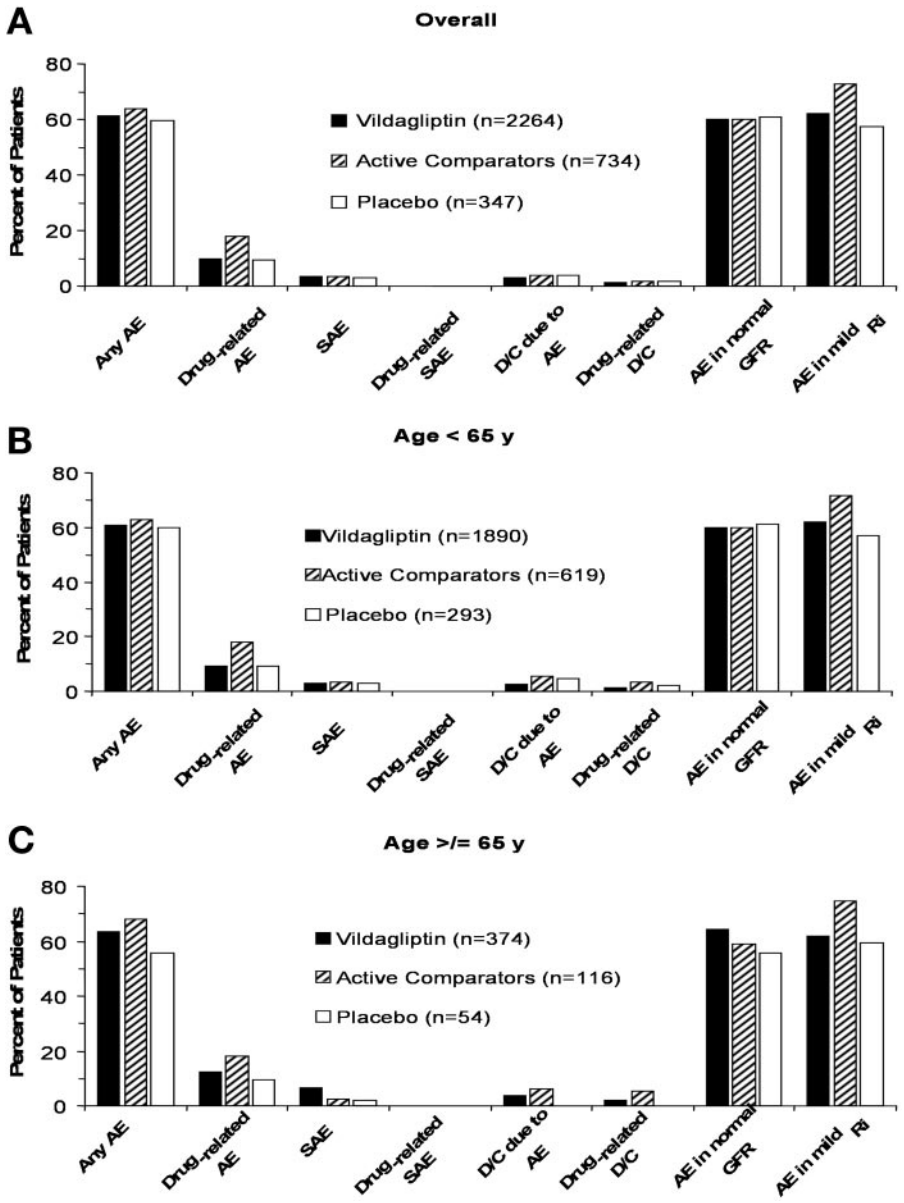

Figure 1— *Adverse events (AE) in patients receiving vildagliptin monotherapy, patients receiving monotherapy with any active comparator, and patients receiving placebo in the overall safety population* (A)*, the subgroup of patients aged <65 years* (B)*, and patients aged ≥65 years* (C)*. D/C, discontinued; RI, renal impairment.*

than in younger (2.6%) vildagliptin-treated patients but were more frequent in both older (6.0%) and younger (5.3%) patients receiving an active comparator.

A summary of the most commonly reported specific adverse events occurring in elderly patients and the incidence of those specific adverse events in the overall safety population and in the younger subgroup is provided in Table A3 of the online appendix. The frequency of any specific adverse event in vildagliptin-treated elderly patients was similar to that in younger patients receiving vildagliptin. In elderly patients receiving vildagliptin, the frequencies of upper respiratory tract infection (6.4%), dizziness (5.3%), and sinusitis (2.4%) were somewhat higher than in the pooled active comparators (3.4, 2.6, and 1.7%, respectively), whereas the frequencies of diarrhea (11.2%), nausea (6.0%), peripheral edema (6.0%), and nasopharyngitis (7.8%) were higher in elderly patients receiving an active comparator than in elderly patients receiving vildagliptin (7.0, 2.9, 1.9, and 1.9%, respectively).

Confirmed hypoglycemia was rare, reported by 9 of 2,264 patients (0.4%) receiving vildagliptin monotherapy, of which 3 were ≥65 years of age (0.8% of the elderly subgroup). All hypoglycemic events in elderly patients were mild in severity; none of the hypoglycemic events led to discontinuation of therapy, and none occurred at night. No severe hypoglycemia occurred in any treatment group. Two of 735 patients (0.3%) receiving an active comparator reported confirmed hypoglycemia, and no patient receiving placebo had a hypoglycemic event.

Four deaths occurred during treatment with vildagliptin (0.2%); two were in the elderly subgroup. In elderly patients receiving vildagliptin, one death was due to ischemic stroke and the other to postoperative bleeding and septic shock after surgery for a small bowel obstruction. Two patients receiving an active comparator died, both of whom were in the younger subgroup; no deaths occurred with placebo.

CONCLUSIONS — The main findings of the present pooled analyses of the efficacy and safety of vildagliptin are that this DPP-4 inhibitor is both effective and well tolerated in elderly patients with type 2 diabetes. Although the elderly population was on average less obese than the younger subgroup, comorbid conditions were much more common; in particular, the older subgroup had a poorer cardiovascular risk profile and higher prevalence of coronary artery disease, as well as a high prevalence of undiagnosed mild renal impairment. These factors and the use of multiple comedications make the management of type 2 diabetes considerably more difficult in elderly individuals. Despite these potential problems, the overall adverse event profile was similar in older and younger patients receiving vildagliptin. It is noteworthy that in patients with mild renal impairment, there was no increase in the incidence of adverse events in older compared with younger patients receiving vildagliptin. Additionally, in older patients, the incidence of adverse events in patients with mild renal impairment was similar to that in patients with normal renal function with vildagliptin treatment. In contrast, the adverse event rate in younger and older patients with mild renal impairment receiving an active comparator was higher than that in patients with normal renal function. Because mild renal impairment is common in elderly patients with type 2 diabetes, although frequently undiagnosed, its impact on the tolerability of any OAD is important to assess and to take into consideration in the choice and intensity of treatment.

In view of the greater propensity for hypoglycemia (and severe hypoglycemia) in elderly patients (2), another important finding is the fact that the incidence of hypoglycemia was very low (0.8%) in elderly patients receiving vildagliptin; no severe hypoglycemia occurred. Although hypoglycemia was even less frequent in patients receiving an active comparator (two patients, 0.3%), it is important to note that the pooled dataset did not include studies with a sulfonylurea or insulin as an active comparator. With regard to hypoglycemia, a recent study of vildagliptin added to insulin therapy is relevant. During 24 weeks of treatment with vildagliptin (100 mg daily) versus placebo added to a stable insulin treatment regimen, it was found that hypoglycemia was significantly less frequent and less severe with vildagliptin than with placebo, and the same trend held in the subgroup of patients aged ≥65 years (15).

Overall, the present safety analysis showed that in elderly patients receiving vildagliptin, there was a slightly lower incidence of any adverse event, drug-related adverse events, and adverse events in those with mild renal impairment than in elderly patients receiving an active comparator. Although there was a slightly higher incidence of SAEs in elderly patients receiving vildagliptin than in those receiving an active comparator, none was suspected to be drug related. Some specific adverse events, such as peripheral edema, nausea, or diarrhea, were less frequently reported with vildagliptin than with the active comparators (metformin and thiazolidinediones).

A relatively benign adverse event profile is an important consideration for treatment of type 2 diabetes in older patients in whom metformin should be used with caution in case altered renal function is present, sulfonylureas present a well-documented risk of hypoglycemia, and thiazolidinediones raise concerns about congestive heart failure. With a new class of OAD, however, particularly one that acts by inhibiting a ubiquitous enzyme such as DPP-4, long-term monitoring with much broader patient exposure will be crucial to further ascertain its safety in elderly patients.

The influence of vildagliptin monotherapy on all efficacy parameters in drug-naive elderly patients with type 2 diabetes was consistently as robust, if not more so, than that in younger patients. Despite lower baseline levels of A1C, FPG, and body weight, in patients aged ≥65 years, the decrease in A1C tended to be greater (Δ −1.2%) than that in patients <65 years of age (Δ −1.0%); the decrease in FPG was significantly greater in the older (Δ −1.5 mmol/l) than in the younger (Δ −1.1 mmol/l) subgroup, and body weight decreased significantly from baseline only in the older subgroup (Δ − 0.9 kg). Further, relative to the younger subgroup, a significantly higher percentage of elderly patients achieved the American Diabetes Association recommended target A1C (<7.0%), both in the whole elderly subgroup (which began with a somewhat lower mean baseline value) and in the population of patients with baseline A1C within 1% of target (in which the elderly and younger subgroups had the same mean baseline A1C of 7.6%).

In view of a report that DPP-4 activity is reduced in elderly subjects (both nondiabetic and those with type 2 diabetes) and the prediction arising from this finding that DPP-4 inhibitors would be less effective in elderly than in younger patients (16), the present efficacy results may be particularly noteworthy and clearly refute that hypothesis. There are at

least two possible explanations for the trend toward enhanced efficacy of vildagliptin in older patients. It may be that the mechanisms underlying development of type 2 diabetes in older patients are more amenable to treatment with a DPP-4 inhibitor. Thus, islet dysfunction, including hyperglucagonemia (17) and postprandial hyperglycemia (18), may play a more significant role in elderly patients with type 2 diabetes, especially when insulin secretion is considered in the context of the prevailing degree of insulin resistance (17). Because vildagliptin acts via GLP-1–mediated improvements in both α- and β-cell function (6) and nutrient intake is the primary stimulus for GLP-1 release, vildagliptin has a pronounced effect to reduce postprandial hyperglycemia (13). This unique mechanism of action could underlie the maintenance of robust efficacy of vildagliptin in elderly patients with type 2 diabetes. Further, the glucose-dependent insulinotropic polypeptide response to nutrient intake is exaggerated in elderly patients with type 2 diabetes (16), which may compensate for the impaired β-cell responsiveness to GIP seen in elderly individuals (19) and in patients with type 2 diabetes (20).

The mechanism by which vildagliptin treatment leads to modest weight loss in elderly individuals is unclear but is not attributable to gastrointestinal upset because gastrointestinal adverse events were reported by few patients and somewhat less frequently in the elderly than in the younger subgroup (e.g., nausea incidence of 1.9 vs. 2.7%, respectively). Moreover, subgroup analyses established that more weight loss was generally seen in more obese subjects, whereas the elderly subjects were on average less obese than the younger subjects. Although vildagliptin treatment does not seem to influence the rate of gastric emptying (21) or satiety in the general population, selective effects of vildagliptin in the elderly on these potential mechanisms or on DPP-4 substrates other than GLP-1 cannot be ruled out.

In summary, although much remains to be understood about the mechanisms underlying some unique aspects of DPP-4 inhibitors in the elderly, vildagliptin monotherapy is effective and appears to be well tolerated in OAD-naive patients aged ≥65 years. Accordingly, the present findings strongly support the continued assessment of vildagliptin to more fully ascertain its safety and efficacy in elderly patients with type 2 diabetes.

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

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

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

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

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

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

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

RESEARCH DESIGN AND METHODS

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

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

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

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

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

Data are *n*, mean ± SD, or *n* (%).

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

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

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

Study assessments

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

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

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

Data analysis

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

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

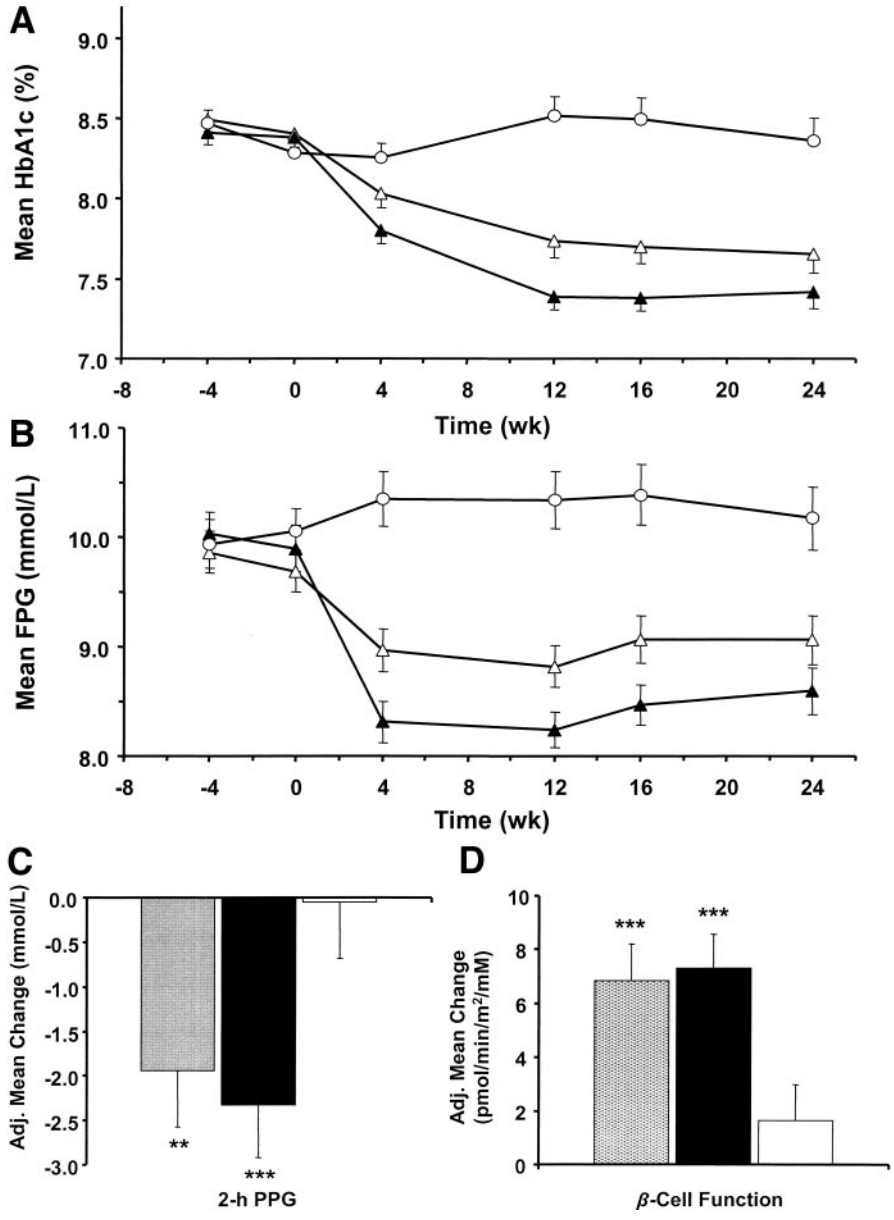

Figure 1—A *and* B*: Mean ± SE A1C (*A*) and FPG* (B) *during 24 weeks of treatment with 50 mg vildagliptin daily (△), 100 mg vildagliptin daily (▲), or placebo (○) in patients with type 2 diabetes continuing stable metformin dose regimen (≥1,500 mg/day).* C *and* D*: Adjusted mean change (±SE) in 2-h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

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

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

Efficacy

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

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

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

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

Standard meal tests

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

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

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

Lipids and body weight

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

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

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

Safety and tolerability

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

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

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

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

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

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

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

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

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

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

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

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

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Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea*

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Aim: To compare the efficacy and tolerability of vildagliptin vs. placebo in patients with type 2 diabetes mellitus (T2DM) who are inadequately controlled [haemoglobin A_{1c} (HbA_{1c}) 7.5 to 11%] with prior sulphonylurea (SU) monotherapy.

Methods: This 24-week, multicentre, randomized, double-blind, placebo-controlled study assessed the effects of the dipeptidyl peptidase-4 inhibitor vildagliptin (50 mg given once or twice daily) vs. placebo added to glimepiride (4 mg once daily) in 515 patients with T2DM. Adjusted mean changes from baseline to end-point (AMΔ) in HbA_{1c}, fasting plasma glucose, fasting lipids and body weight were compared by analysis of covariance.

Results: The between-group difference (vildagliptin − placebo) in AMΔ HbA_{1c} was $-0.6 \pm 0.1\%$ in patients receiving vildagliptin 50 mg daily and $-0.7 \pm 0.1\%$ in those receiving 100 mg daily ($p < 0.001$ vs. placebo for both). Greater efficacy was seen in patients ≥65 years of age ($-0.7 \pm 0.1\%$ and $-0.8 \pm 0.2\%$ for 50 and 100 mg daily respectively) and in patients with baseline $HbA_{1c} > 9\%$ ($\Delta = -1.0 \pm 0.2\%$ and $-0.9 \pm 0.2\%$ for 50 and 100 mg daily respectively). Relative to placebo, patients receiving vildagliptin also had improvements in β-cell function and postprandial glucose, with small changes in fasting lipids and body weight. The incidences of adverse events (AEs) (67.1, 66.3 and 64.2%) and serious AEs (2.9, 2.4 and 5.1%) were similar in patients receiving 50 mg vildagliptin, 100 mg vildagliptin or placebo respectively. The incidence of hypoglycaemic events was low but slightly higher in the group receiving vildagliptin 100 mg (3.6%) than in the group receiving vildagliptin 50 mg (1.2%) or placebo (0.6%).

Conclusions: In patients with T2DM inadequately controlled with prior SU monotherapy, addition of vildagliptin (50 or 100 mg daily) to glimepiride (4 mg once daily) improves glycaemic control and is well tolerated. Addition of vildagliptin 50 mg daily to SU monotherapy may be a particularly attractive therapy in elderly patients.

Keywords: dipeptidyl peptidase-4, glimepiride, HbA_{1c}, incretin hormones, vildagliptin
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Introduction

Vildagliptin is a potent and selective dipeptidyl peptidase (DPP)-4 inhibitor [1] that improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) by increasing both α- and β-cell responsiveness to glucose [2,3]. Efficacy and tolerability of vildagliptin have been demonstrated in this population both as monotherapy

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[4,5] and as add-on in patients who have been inadequately controlled with metformin [6,7], pioglitazone [8] or insulin [9].

The sulphonylureas (SUs) are commonly used as first-line therapy for T2DM; however, despite good initial efficacy, this drug class is associated with progressive worsening of blood glucose control over time, requiring additional drug therapy for most patients [10]. Because vildagliptin acts through increasing plasma levels of the active forms of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), it improves islet function by a mechanism independent of the SU receptor. This is manifested as increased glucose sensing by both α and β cells [2,3,11–13]. Thus, vildagliptin may be effective even in patients already receiving an SU. The purpose of the present randomized, placebo-controlled trial was to ascertain the efficacy and tolerability of vildagliptin (50 or 100 mg daily) given as an add-on to glimepiride (4 mg once daily) in patients with T2DM and inadequate glycaemic control [haemoglobin A_{1c} (HbA_{1c}) 7.5–11%) with prior SU monotherapy.

Methods

Study Design

This was a multicentre, randomized, double-blind, placebo-controlled study conducted at 114 centres in the USA (88), Sweden (9), Finland (7), Argentina (6) and Lithuania (4), enrolling patients with T2DM inadequately controlled on SU monotherapy (≥7.5 mg glyburide, or glipizide once daily or equivalent, or ≥2 mg glimepiride once daily). Each patient attended one screening visit (week 4), during which inclusion/exclusion criteria were assessed, and any patient not previously receiving glimepiride 4 mg once daily was switched to this SU regimen. Eligible patients were randomized at visit 2 (week 0, baseline) to receive vildagliptin 50 mg daily (given as a single dose), vildagliptin 100 mg daily (given in divided dose) or placebo, each as add-on to glimepiride 4 mg once daily. At visit 2, all eligible patients were assigned a randomization number linked to one of the treatment groups. A randomization list was produced using a health authority–inspected and validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. After randomization, the glimepiride dose could be reduced to 2 mg once daily, according to predefined criteria if hypoglycaemia occurred. Efficacy and tolerability were assessed during four additional visits, at weeks 4, 12, 16 and 24 of treatment.

Study Population

The study enrolled patients with T2DM who were inadequately controlled on SU monotherapy, with a baseline HbA_{1c} of 7.5–11%. Patients were required to have been treated with an SU for ≥3 months and with a stable dose for ≥4 weeks before the screening visit. Male or female patients (females of childbearing potential were required to use a medically approved contraceptive method), 18–80 years of age, with a body mass index (BMI) of 22–45 kg/m^2 and fasting plasma glucose (FPG) < 15 mmol/l were eligible to participate.

Patients were excluded if they had a history of type 1 or secondary forms of diabetes, myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months. Congestive heart failure (New York Heart Association class III or IV), liver disease such as cirrhosis or chronic active hepatitis or use of any oral antidiabetic drug other than an SU within the past 2 months also precluded participation. Patients with any of the following laboratory abnormalities were also excluded: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal (ULN), direct bilirubin >1.3 times the ULN, serum creatinine levels >220 μmol/l, thyroid-stimulating hormone outside the normal range or fasting triglycerides (TGs) >7.9 mmol/l.

Study Assessments

HbA_{1c}, FPG, body weight and vital signs were measured at each study visit. Fasting lipids [TGs, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol] were measured, and ECGs were performed at the screening visit (week 4) and at weeks 0, 12 and 24. Safety laboratory assessments were made at each study visit except that at week 16.

Standard breakfast meal challenges (500 kcal; 60% carbohydrate, 30% fat and 10% protein) were performed at baseline (week 0) and at week 24 in the subset of patients (~16%) volunteering to participate. Samples for measurement of glucose, insulin and C-peptide were obtained at times −20, 0, 15, 30, 60, 90, 120, 180 and 240 min relative to the meal (provided immediately after the 0-min sample and consumed within 15 min). Insulin secretory rate (ISR) was calculated by deconvolution of C-peptide levels [14]. The 2-h area under the curve (AUC) for ISR and glucose was calculated using the trapezoidal method, and the ratio of ISR $AUC_{0–2\ h}$ to glucose $AUC_{0–2\ h}$ was used as an index of β-cell function. Homeostasis model assessment insulin resistance index (HOMA-IR) and a meal

test–derived insulin sensitivity index (ISI) were used as static and dynamic measures of insulin sensitivity.

Adverse events (AEs) were recorded at each visit and assessed for severity and possible relationship to study medication. All patients were provided with home blood glucose monitors and supplies and were instructed in their use at study entry. Hypoglycaemia was defined as the presence of symptoms suggestive of hypoglycaemia confirmed by self-monitored blood glucose <3.1 mmol/l plasma glucose equivalent. Severe hypoglycaemia was defined as any episode requiring assistance from another person. Increases in ALT, AST or direct bilirubin ≥3 times the ULN were considered to be notable.

All laboratory assessments were made by central laboratories. All assessments other than HbA_{1c} were performed by Bioanalytical Research Corporation (BARC-US, Lake Success, NY, USA, or BARC-EU, Ghent, Belgium). Measurements of HbA_{1c} were performed by BARC-EU, Diabetes Diagnostics Laboratory (DDL, Columbia, MO, USA) or Covance-US (Indianapolis, IN, USA). All samples from any single patient were analysed by the same laboratory. Assays were performed according to standardized and validated procedures based on Good Laboratory Practice.

Data Analysis

The primary efficacy variable was the change from baseline in HbA_{1c} at study end-point using last observation carried forward for patients who discontinued early. Secondary efficacy parameters included FPG, fasting plasma lipids, body weight and meal test–derived parameters. The primary efficacy analyses were performed with data from patients who (i) had a screening HbA_{1c} value ≥7.4%, (ii) received at least one dose of study medication and (iii) had a baseline and at least one postbaseline HbA_{1c} measurement. This population is referred to as the primary intent-to-treat (ITT) population and was prespecified as the main efficacy population. The safety population comprised all patients exposed to at least one dose of study drug and who had at least one postbaseline safety assessment.

A total sample size of 345 randomized patients (in 1 : 1 : 1 allocation ratio to vildagliptin 50 mg, vildagliptin 100 mg and placebo) was required to allow for a ~10% dropout rate and provide at least 90% power to detect a clinically meaningful difference in HbA_{1c} (0.5%), assuming a standard deviation of 1 and an overall significance level of 5% to declare the superiority of vildagliptin over placebo for the effect of reducing HbA_{1c} from baseline after 24 weeks of treatment, adjusting for multiple comparisons (two tests at $p = 0.025$).

Changes from baseline in primary and secondary end-points were analysed using an analysis of covariance model, with treatment and pooled centre as the classification variables and baseline value as the covariate. Analyses were carried out using two-tailed tests and a statistical significance level of 0.05. For HbA_{1c} and FPG, multiple testing was adjusted for using Hochberg's step-up procedure to maintain an overall two-sided significance level of 0.05 [15]. Prespecified subgroup analyses of changes from baseline in HbA_{1c} were also performed according to baseline HbA_{1c} (≤9 and >9%) and age (<65 and ≥65 years). Responder rates in each treatment group (percentage of patients achieving end-point $HbA_{1c} < 7\%$ and percentage of patients experiencing a reduction of at least 0.7%) were compared by chi-squared tests.

Ethics and Good Clinical Practice

All participants provided written informed consent after a full explanation of study procedures, risks and benefits. The study protocol was approved by an 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

Figure 1 depicts patient disposition from screening through study end-point. A total of 515 patients were randomized and 408 comprised the primary ITT population. A higher proportion of patients in the placebo group (25%) than in either vildagliptin groups (14–16%) discontinued prematurely, primarily because of unsatisfactory therapeutic effect (11.1%) or withdrawal of consent (8.3%). Only five patients had their glimepiride dose reduced to 2 mg daily because of hypoglycaemia (three patients from the vildagliptin 100 mg daily group and one patient each from the other two groups).

Table 1 summarizes the baseline demographic and background characteristics of these patients. The groups were well balanced at baseline, with a mean HbA_{1c} of 8.5% and FPG of 10.4 mmol/l. Participants were predominantly Caucasian and obese (mean BMI = 31.3 kg/m^2), with nearly one quarter being severely obese. Mean age was 58 years, and more than 25% of participants were ≥65 years of age. In the combined cohort, the mean disease duration was 7.1 years and mean duration of SU use was approximately 4 years.

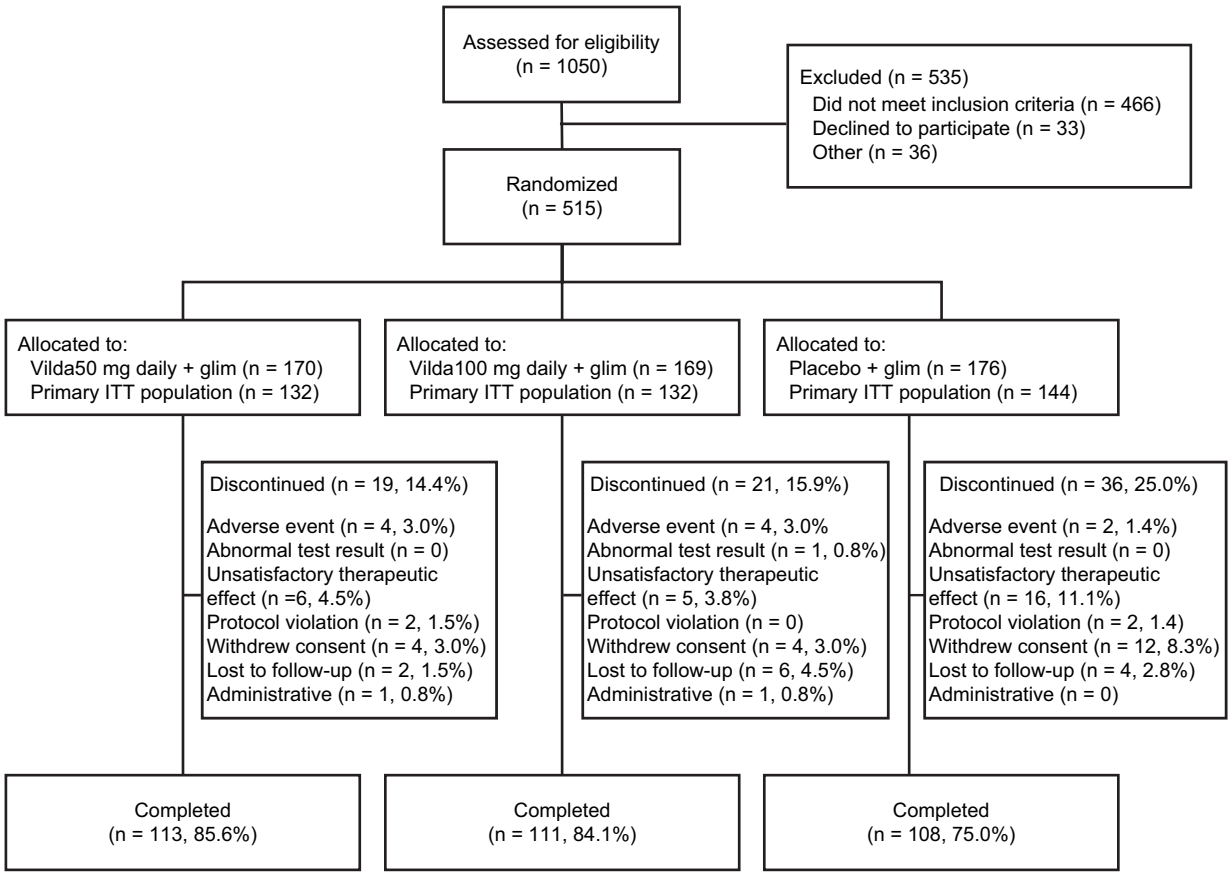

Fig. 1 Patient flow for study. Glim, glimepiride; vilda, vildagliptin.

Efficacy

Figure 2 depicts the mean HbA_{1c} during 24-week treatment with vildagliptin (50 or 100 mg daily) or placebo added to glimepiride in the primary ITT population. With either vildagliptin dose regimen added to glimepiride 4 mg daily, HbA_{1c} decreased by week 4 and reached a maximum reduction by week 12, while HbA_{1c} remained stable in patients receiving placebo and continuing glimepiride. The AMΔ HbA_{1c} was $-0.58 \pm 0.10\%$ in the group receiving vildagliptin 50 mg, -0.63 ± 0.09 in the group receiving vildagliptin 100 mg daily and $+0.07 \pm 0.09\%$ in patients receiving placebo. The between-group difference (vildagliptin − placebo) in the AMΔ HbA_{1c} was $-0.64 \pm 0.13\%$ in patients receiving vildagliptin 50 mg daily ($p < 0.001$ vs. placebo) and $-0.70 \pm 0.13\%$ in those receiving vildagliptin 100 mg daily ($p < 0.001$ vs. placebo).

Figure 3 depicts the mean changes from baseline to end-point in HbA_{1c} in patients <65 and ≥65 years of age (panel A) and in the subgroups of patients with baseline HbA_{1c} above and below 9% (panel B). In this prespecified subgroup analysis, greater reductions in HbA_{1c} were seen in those patients with higher HbA_{1c} at baseline. In addition, despite slightly lower baseline HbA_{1c} levels in older patients receiving vildagliptin compared with their younger counterparts, the mean change from baseline in HbA_{1c} was greater in older patients receiving vildagliptin.

A significantly greater proportion of patients receiving add-on therapy with vildagliptin 50 mg daily (21.2%, $p = 0.039$) or 100 mg daily (24.8%, $p = 0.006$) achieved an end-point $HbA_{1c} < 7\%$ when compared with placebo (12%). Similarly, a reduction in HbA_{1c} of ≥0.7% was experienced by a significantly greater percentage of patients receiving vildagliptin 50 mg daily (47.0%, $p < 0.001$) or 100 mg daily (50.8%, $p < 0.001$) compared with placebo (19.4%).

FPG, Lipids and Body Weight

Baseline FPG averaged 10.5 mmol/l in both vildagliptin treatment groups and 10.3 mmol/l in placebo group.

Table 1 Baseline characteristics of the primary ITT population

	Vildagliptin 50 mg daily + glimepiride	Vildagliptin 100 mg daily + glimepiride	Placebo + glimepiride
n	132	132	144
Age (years), mean ± s.d.	58.6 ± 10.6	58.2 ± 11.1	57.9 ± 10.5
Age group			
<65 years	91 (68.9)	97 (73.5)	106 (73.6)
≥65 years	41 (31.1)	35 (26.5)	38 (26.4)
Sex			
Male	78 (59.1)	79 (59.8)	84 (58.3)
Female	54 (40.9)	53 (40.2)	60 (41.7)
Race			
Caucasian	91 (68.9)	93 (70.5)	97 (67.4)
Hispanic/Latino	24 (18.2)	24 (18.2)	27 (18.8)
Black	14 (10.6)	11 (8.3)	15 (10.4)
All other	3 (2.3)	4 (3.0)	5 (3.4)
BMI (kg/m^2), mean ± s.d.	32.2 ± 4.9	30.8 ± 5.3	31.0 ± 5.5
HbA_{1c} (%), mean ± s.d.	8.5 ± 0.9	8.6 ± 1.0	8.5 ± 1.0
HbA_{1c} group (%)			
≤8	40 (30.3)	48 (36.4)	59 (41.0)
>8	92 (69.7)	84 (63.6)	85 (59.0)
≤9	100 (75.8)	93 (70.5)	99 (68.8)
>9	32 (24.2)	39 (29.5)	45 (31.3)
FPG (mmol/l), mean ± s.d.	10.5 ± 3.0	10.5 ± 2.7	10.3 ± 2.9
Disease duration (years), mean ± s.d.	6.9 ± 5.2	6.7 ± 5.3	7.8 ± 5.8
Duration of sulphonylurea use (months), mean ± s.d.	47.7 ± 42.7	45.8 ± 44.4	52.6 ± 56.0

BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; ITT, intent-to-treat.
Values are expressed as n (%) unless indicated.

During the 24-week study, FPG tended to decrease in patients receiving vildagliptin 50 mg daily (AMΔ = −0.3 ± 0.2 mmol/l) or 100 mg daily (AMΔ = −0.4 ± 0.2 mmol/l) and tended to increase in patients receiving placebo added to glimepiride (AMΔ = +0.2 ± 0.2 mmol/l). However, the between-group difference in the AMΔ FPG did not achieve statistical significance in either the group receiving vildagliptin 50 mg daily (−0.5 ± 0.3 mmol/l, p = 0.118) or the group receiving 100 mg daily (−0.6 ± 0.3, p = 0.056).

Fasting lipid levels at baseline were similar in each treatment group and changed minimally (by ≤3%) during the 24-week study. Approximately one third of patients in each group were receiving concomitant therapy with lipid-lowering agents. When adjusting for this factor, there was no significant difference between groups in any fasting lipid parameter.

In the primary ITT population, body weight at baseline averaged 91.5 ± 1.6, 87.3 ± 1.6 and 89.4 ± 1.6 kg in patients randomized to vildagliptin 50 mg daily, vildagliptin 100 mg daily and placebo respectively. Body weight decreased slightly in patients receiving placebo (AMΔ = −0.4 ± 0.3 kg) or vildagliptin 50 mg daily (AMΔ = −0.1 ± 0.3 kg, p = 0.409 vs. placebo). Body weight increased modestly in patients receiving vildagliptin 100 mg daily added to glimepiride (AMΔ = +1.3 ± 0.3 kg, p < 0.001 vs. placebo).

Prandial Glucose and β-cell Function

Several parameters describing postprandial glucose (PPG) and β-cell function were derived from standard breakfast meal tests performed at baseline and end-point in 64 patients (~16% of primary ITT population), with comparable numbers of patients from each treatment arm. Relative to placebo, prandial insulin levels increased significantly and similarly in patients receiving vildagliptin 50 or 100 mg daily. The between-treatment difference in the AMΔ insulin $AUC_{0–4\ h}$ was 160 ± 71 pmol/l h (p = 0.028) in patients receiving vildagliptin 50 mg daily and 178 ± 72 pmol/l h (p = 0.017) in those receiving 100 mg daily.

The peak prandial glucose excursion (PPGE) decreased in vildagliptin-treated patients and increased slightly in patients receiving placebo added to glimepiride. At baseline, the PPGE averaged 6.5 mmol/l in patients randomized to vildagliptin 50 mg daily and 5.8 mmol/l in other two groups. The between-group difference in the AMΔ PPGE was −1.5 ± 0.5 mmol/l (p = 0.008 vs. placebo) in patients receiving vildagliptin 50 mg daily and

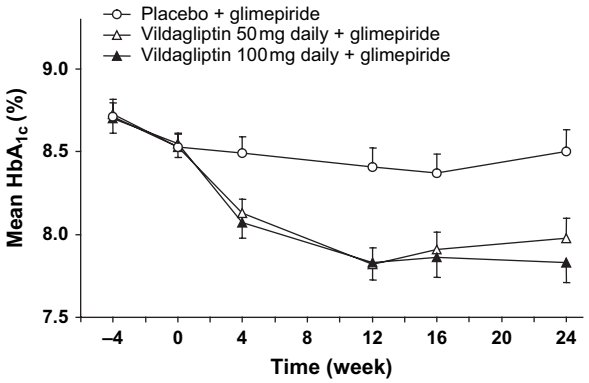

Fig. 2 Mean (± s.e.) HbA_{1c} during 24-week treatment with vildagliptin 50 mg daily (open triangles, n = 132 at baseline, n = 113 at week 24), vildagliptin 100 mg daily (closed triangles, n = 132 at baseline, n = 110 at week 24) or placebo (open circles, n = 144 at baseline, n = 111 at week 24), each in combination with glimepiride 4 mg once daily in patients with type 2 diabetes mellitus not adequately controlled by prior sulphonylurea monotherapy. HbA_{1c}, haemoglobin A_{1c}.

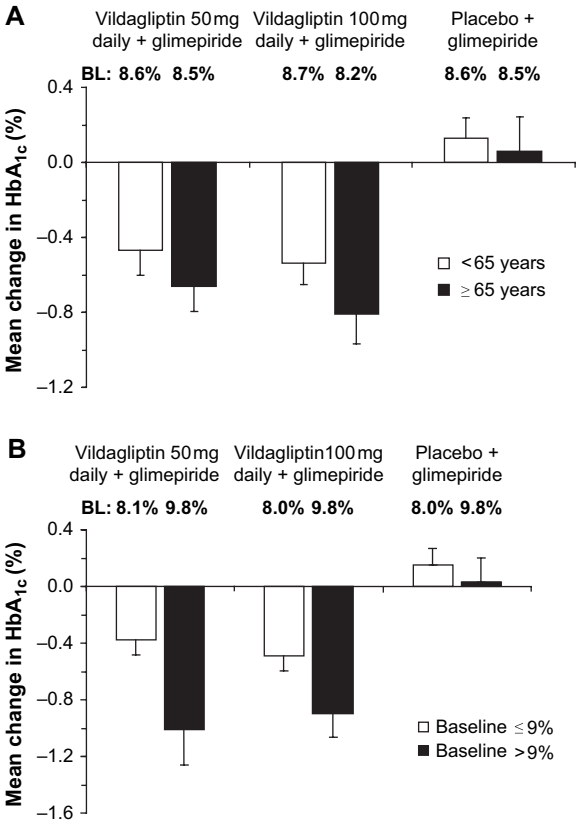

Fig. 3 (A) Mean (± s.e.) change from baseline to end-point in haemoglobin A_{1c} (HbA_{1c}) in patients aged <65 years (open bars; n = 91, 97 and 106; mean baseline HbA_{1c} ≈ 8.6% for all treatment groups) and in patients aged ≥65 years (closed bars; n = 41, 35 and 38; mean baseline HbA_{1c} = 8.5, 8.2 and 8.5% for vildagliptin 50 mg daily, 100 mg daily or placebo respectively). (B) Mean (± s.e.) change from baseline to end-point in HbA_{1c} in patients with lower baseline HbA_{1c} (open bars; n = 100, 93 and 99; mean baseline HbA_{1c} ≈ 8.0% for all treatment groups) and in patients with higher baseline HbA_{1c} (closed bars; n = 32, 39 and 45; mean baseline HbA_{1c} = 9.8% for all treatments).

−0.9 ± 0.5 mmol/l (p = 0.085 vs. placebo) in patients receiving 100 mg daily.

Beta-cell function was quantified by calculating the ISR $AUC_{0–2\ h}$/glucose $AUC_{0–2\ h}$ (ISR/G). At baseline, this parameter averaged 17.5 ± 1.3 pmol/min/m^2/mM in patients randomized to vildagliptin 50 mg daily, 19.4 ± 1.7 pmol/min/m^2/mM in those randomized to vildagliptin 100 mg daily and 19.7 ± 1.3 pmol/min/m^2/mM in patients randomized to placebo. As illustrated in figure 4, β-cell function as assessed by ISR/G improved in vildagliptin-treated patients and declined modestly in patients receiving placebo as an add-on to glimepiride. The between-group difference in the AMΔ ISR/G was 4.1 ± 1.8 pmol/min/m^2/mM in patients receiving vildagliptin 50 mg daily (p = 0.024 vs. placebo) and 4.6 ± 1.8 pmol/min/m^2/mM (p = 0.014 vs. placebo) in those receiving 100 mg daily.

Relative to placebo, neither static (e.g. HOMA-IR) nor dynamic (i.e. ISI) measures of insulin resistance changed significantly. However, consistent with improved β-cell function as assessed by ISR/G, both vildagliptin treatment regimens significantly decreased the fasting proinsulin to insulin ratio (data not shown).

Tolerability

The overall incidence of AEs was similar across all treatment groups, and there was a similar broad distribution among primary system organ classes. Table 2 summarizes the most common AEs during the 24-week study. Although a number of the more common AEs were reported with greater frequency in one of the vildagliptin add-on groups, no dose-related effects were observed. Asthenia, nasopharyngitis and upper respiratory tract infection were more common in both vildagliptin groups compared with placebo, while influenza, insomnia and vomiting were more common in the placebo group compared with the vildagliptin groups. Most AEs were mild or moderate and not suspected to be related to study medications. Serious AEs (SAEs) were reported by a higher percentage of the placebo group

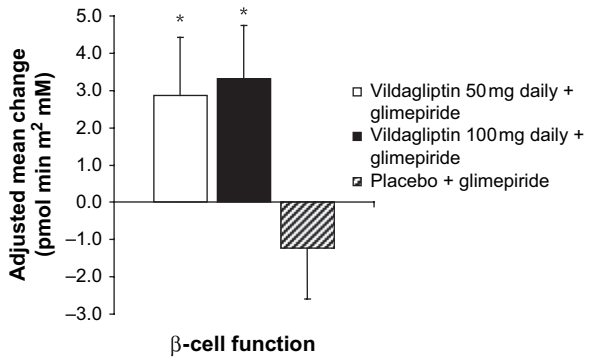

Fig. 4 Adjusted mean (± s.e.) change from baseline to endpoint in β-cell function during 24-week treatment with vildagliptin 50 mg daily (open bar, n = 20), vildagliptin 100 mg daily (closed bar, n = 20) or placebo (hatched bar, n = 23), each in combination with glimepiride 4 mg daily in patients with type 2 diabetes mellitus not adequately controlled by sulphonylurea monotherapy. The insulin secretion rate $AUC_{0-2\ h}$ divided by glucose $AUC_{0-2\ h}$ was used as an index of β-cell function. *$p < 0.05$. AUC, area under the curve.

(5.1%) vs. either the low-dose (2.9%) or the high-dose (2.4%) vildagliptin group. The only SAE reported by more than a single patient in any treatment group was basal cell carcinoma, which was reported by two patients receiving vildagliptin 50 mg daily. Only one SAE – a case of severe hypoglycaemia in the placebo group – was suspected by the investigator to be related to study medication. AEs led to study discontinuation in a slightly higher percentage of patients in the group receiving vildagliptin 50 mg (2.4%) and 100 mg (3.0%) daily than in the placebo group (1.7%).

Hypoglycaemia was reported more frequently in the group receiving vildagliptin 100 mg daily (6/169, 3.6%) than in the group receiving vildagliptin 50 mg daily (2/170, 1.2%) or in the placebo group (1/176 = 0.6%). These events were generally associated with a precipitating event (i.e. missed/delayed meal and strenuous exercise) and occurred several hours after the morning doses of study medication.

There were no major changes or consistent trends in any haematological, biochemical or urinalysis parameter or vital signs. One patient in each vildagliptin add-on group (0.6%) experienced a notable increase in ALT; no vildagliptin-treated patient experienced a notable increase in AST, and one patient receiving vildagliptin 100 mg daily (0.6%) experienced a notable increase in bilirubin. Two patients receiving placebo (1.2%) experienced notable increases in ALT and AST and no patient receiving placebo experienced a notable increase in bilirubin. The frequency of treatment-emergent ECG changes was low and comparable among all treatment groups. No deaths occurred during the study.

Table 2 Common adverse events (AEs) occurring in >3% of any treatment group*

	Vildagliptin 50 mg daily + glimepiride (n = 170), n (%)	Vildagliptin 100 mg daily + glimepiride (n = 169), n (%)	Placebo + glimepiride (n = 176), n (%)
Any AE	114 (67.1)	112 (66.3)	113 (64.2)
Asthenia	14 (8.2)	10 (5.9)	4 (2.3)
Nasopharyngitis	8 (4.7)	10 (5.9)	4 (2.3)
Upper respiratory tract infection	11 (6.5)	9 (5.3)	3 (1.7)
Dizziness	15 (8.8)	8 (4.7)	7 (4.0)
Influenza	7 (4.1)	8 (4.7)	13 (7.4)
Headache	7 (4.1)	6 (3.6)	4 (2.3)
Hypoglycaemia	2 (1.2)	6 (3.6)	1 (0.6)
Nausea	3 (1.8)	6 (3.6)	6 (3.4)
Tremor	12 (7.1)	6 (3.6)	5 (2.8)
Diarrhoea	5 (2.9)	4 (2.4)	8 (4.5)
Hyperhidrosis	7 (4.1)	4 (2.4)	4 (2.3)
Sinusitis	8 (4.7)	4 (2.4)	5 (2.8)
Back pain	10 (5.9)	3 (1.8)	6 (3.4)
Pain in extremity	6 (3.5)	3 (1.8)	8 (4.5)
Insomnia	1 (0.6)	2 (1.2)	8 (4.5)
Paraesthesia	3 (1.8)	2 (1.2)	6 (3.4)
Fatigue	7 (4.1)	1 (0.6)	3 (1.7)
Vomiting	2 (1.2)	1 (0.6)	6 (3.4)
Hyperlipidaemia	6 (3.5)	0	1 (0.6)
Any serious AE	5 (2.9)	4 (2.4)	9 (5.1)
Discontinued because of AE	4 (2.4)	5 (3.0)	3 (1.7)

*Safety population.

Discussion

The main findings of this study were that in patients with T2DM inadequately controlled by SU monotherapy, addition of the DPP-4 inhibitor vildagliptin (50 or 100 mg daily) produced a statistically significant and clinically meaningful reduction in HbA_{1c}, and the combination of either vildagliptin dose regimen with glimepiride had a good overall tolerability profile. Furthermore, when added to glimepiride 4 mg daily, vildagliptin 50 mg daily was as efficacious as 100 mg daily but did not cause weight gain and was associated with a very low incidence of mild hypoglycaemia.

The present findings regarding the efficacy of vildagliptin are in general agreement with a recent report on another DPP-4 inhibitor, sitagliptin, added to glimepiride [16] and an earlier study in which the injectable incretin mimetic, exenatide, was added to SU monotherapy [17], but there are some notable exceptions. With sitagliptin (100 mg once daily) added to glimepiride (≥4 mg/day), the placebo-subtracted ΔHbA_{1c} after 24-week treatment was −0.6%, essentially identical to the present findings with vildagliptin 50 or 100 mg daily. However, although baseline HbA_{1c} levels (~8.4%) were similar to those in the present study (~8.5%), much of the treatment effect with sitagliptin was because of a deterioration of glycaemic control in the placebo group. In the present trial, nearly all of the placebo-subtracted change in HbA_{1c} reflected a decrease from baseline with vildagliptin, indicating that participants had stable glycaemic control at study entry. A more important difference between these studies is that addition of sitagliptin to glimepiride was associated with a substantially higher incidence of hypoglycaemia (7.5 vs. 2.8% for placebo) and significant weight gain (1.1 kg). Increased incidence of hypoglycaemia was also seen with vildagliptin 100 mg daily (3.6 vs. 0.6% for placebo), and this dose also led to some weight gain (1.3 kg). However, the 50-mg daily dose of vildagliptin was associated with a low incidence of hypoglycaemia (1.2%) and no weight gain (−0.1 kg), despite efficacy equivalent to that seen with the 100-mg daily dose of either sitagliptin [16] or vildagliptin.

In the study in which exenatide (5 or 10 μg twice daily) was given as an add-on to SU monotherapy (glimepiride 4 mg/day or equivalent) for 30 weeks [17], the lower dose elicited a placebo-adjusted reduction in HbA_{1c} of 0.6% but with a 14% incidence of hypoglycaemia (vs. 3% for placebo). The 10-μg twice daily dose regimen elicited greater efficacy (−1.0% relative to placebo) but with even more hypoglycaemia (36%). Consistent with the present findings with vildagliptin, greater efficacy was seen in patients with a high baseline HbA_{1c}. In contrast to findings with DPP-4 inhibitors, which were either weight neutral (50 mg vildagliptin) or led to modest weight gain (100 mg of either vildagliptin or sitagliptin), there was modest weight loss with the 10-μg twice daily dose regimen of exenatide (−1.6 vs. −0.6 kg with placebo).

At least three questions arise from the findings of the present study. First, why is there no dose response for the HbA_{1c}-lowering effect of vildagliptin? Second, why is there no significant effect on FPG? And third, why is there an increased incidence of hypoglycaemia with the 100-mg daily dose when there is, on average, no additional efficacy? Regarding the overall efficacy of vildagliptin added to glimepiride, it should be recognized that a reduction in HbA_{1c} reflects, in essence, the sum of the effects on PPG and FPG. Because there was no significant effect of vildagliptin to reduce FPG in this study, any dose–response for HbA_{1c} reduction would require that 100 mg daily (50 mg twice daily) exerts a larger effect than 50 mg on PPG. A very simple explanation for the lack of a differential effect of 50 and 100 mg daily on PPG is that 50 mg vildagliptin was given before the breakfast meal test with either dose regimen and with doses as low as 10 mg; vildagliptin elicits essentially complete inhibition of DPP-4 for at least 4 h, that is throughout the entire postmeal sampling period. This results in similar AUCs for GLP-1, GIP, insulin, glucagon and glucose during oral glucose tolerance test, irrespective of vildagliptin dose. Furthermore, because a single 50-mg dose of vildagliptin elicits >80% inhibition of DPP-4 activity for at least 12 h [18], the benefit to be derived from the second dose of vildagliptin in the 100 mg daily treatment arm would not come from reduced PPG after the evening meal but rather from decreasing glucose levels during the overnight postabsorptive period.

Although it has been shown that a single dose of vildagliptin given before the evening meal increases active GLP-1 and insulin, decreases plasma glucagon and reduces endogenous glucose production throughout the overnight period [11], the present finding that neither vildagliptin dose regimen significantly decreased FPG when added to glimepiride suggests that the presence of an SU decreases either the secretion of or islet responsiveness to GLP-1 during the postabsorptive period. The modest trend towards reduced FPG with vildagliptin, and the magnitude of the reduction (−0.5 to −0.6 mmol/l), is consistent with alleviation of 'glucose toxicity' through the improved prandial glycaemic control.

At the levels achieved through DPP-4 inhibition, the insulinotropic effects of GLP-1 are strictly glucose dependent and, accordingly, hypoglycaemia is seldom seen

when vildagliptin is given as monotherapy [4,5,19,20]. An explanation for the hypoglycaemia seen in the present study with vildagliptin 100 mg daily added to glimepiride (also seen with sitagliptin [16]) may be provided by a recent article by de Heer and Holst [21]. Using the *in situ* perfused rat pancreas, these authors found that SUs appear to 'uncouple' the glucose dependence of GLP-1's effects on pancreatic hormone secretion. Thus, in the presence of an SU, increasing active GLP-1 through inhibition of DPP-4 may increase insulin and suppress glucagon secretion regardless of the prevailing glucose level, and this could predispose to mild hypoglycaemia. However, a recent study demonstrated that in healthy volunteers, vildagliptin did not exacerbate the more serious hypoglycaemia induced by SU administration in these non-diabetic subjects [22]. There is no clear explanation for the greater incidence with vildagliptin 100 vs. 50 mg daily, but loss of glucose dependence may underlie the much higher incidence of hypoglycaemia seen with the exenatide when combined with an SU [17]. It should also be noted that in the present study, the number of patients who experienced hypoglycaemia was small (six vs. two patients), and the difference between treatment groups may just reflect achievement of better glycaemic control in those individual patients. The fact that all events were mild suggests some degree of glucose dependency.

As seen in previous studies of monotherapy [4,5,19,20] or in combination with metformin [6] or a thiazolidinedione (TZD) [8], vildagliptin was well tolerated when combined with an SU. The overall incidence of AEs in vildagliptin-treated patients was similar to that in patients receiving placebo; there was a slightly higher incidence of discontinuations because of an AE with vildagliptin but a somewhat higher incidence of SAEs in patients receiving placebo. Notable increases in liver enzymes were rare but slightly more common in patients receiving placebo (two patients, 1.2%) than in vildagliptin-treated patients (one patient, 0.6% in both groups receiving 50 mg and 100 mg vildagliptin treatment).

The overall favourable tolerability profile of vildagliptin added to an SU, together with the observation of somewhat enhanced efficacy of vildagliptin in patients $\geq$65 years of age, suggests that vildagliptin may be an appropriate agent to use in elderly patients failing to achieve adequate glycaemic control with SU monotherapy. For a variety of reasons, treatment of T2DM in elderly patients can be difficult [23], and therapeutic options may be limited by the existence of comorbid conditions. The current findings suggest that a single 50-mg daily dose of vildagliptin may provide substantial additional efficacy but without the weight gain often seen with TZDs or the gastrointestinal upset that may accompany acarbose or metformin [24]. Because the 100-mg daily dose provided little additional efficacy, but was associated with modestly increased incidence of mild hypoglycaemia and modest weight gain, there would be no rationale for using the higher dose. However, it is possible that further experience would identify patients who would benefit from the 100-mg daily dose as an add-on to SU therapy.

In summary, this study has shown that in patients with T2DM inadequately controlled with SU monotherapy, the addition of vildagliptin improves β-cell function and, accordingly, prandial glucose control, resulting in a clinically meaningful reduction in HbA_{1c}. Vildagliptin was generally well tolerated, and the 50-mg daily dose was as effective as 100-mg daily dose but caused no weight gain and was associated with a very low incidence (~1%) of mild hypoglycaemia. Because of its independent mechanism of action on the islet, vildagliptin may be a useful adjunct to SUs, particularly in elderly patients with T2DM.

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Appendix

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Comparison of Vildagliptin and Rosiglitazone Monotherapy in Patients With Type 2 Diabetes

A 24-week, double-blind, randomized trial

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OBJECTIVE — To compare the efficacy and tolerability of vildagliptin and rosiglitazone during a 24-week treatment in drug-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a double-blind, randomized, active-controlled, parallel-group, multicenter study of 24-week treatment with vildagliptin (100 mg daily, given as equally divided doses; $n = 519$) or rosiglitazone (8 mg daily, given as a once-daily dose; $n = 267$).

RESULTS — Monotherapy with vildagliptin and rosiglitazone decreased A1C (baseline = 8.7%) to a similar extent during the 24-week treatment, with most of the A1C reduction achieved by weeks 12 and 16, respectively. At end point, vildagliptin was as effective as rosiglitazone, improving A1C by −1.1 ± 0.1% ($P < 0.001$) and −1.3 ± 0.1% ($P < 0.001$), respectively, meeting the statistical criterion for noninferiority (upper-limit 95% CI for between-treatment difference ≤0.4%). Fasting plasma glucose decreased more with rosiglitazone (−2.3 mmol/l) than with vildagliptin (−1.3 mmol/l). Body weight did not change in vildagliptin-treated patients (−0.3 ± 0.2 kg) but increased in rosiglitazone-treated patients (+1.6 ± 0.3 kg, $P < 0.001$ vs. vildagliptin). Relative to rosiglitazone, vildagliptin significantly decreased triglycerides, total cholesterol, and LDL, non-HDL, and total-to-HDL cholesterol (−9 to −16%, all $P \leq 0.01$) but produced a smaller increase in HDL cholesterol (+4 vs. +9%, $P = 0.003$). The proportion of patients experiencing an adverse event was 61.4 vs. 64.0% in patients receiving vildagliptin and rosiglitazone, respectively. Only one mild hypoglycemic episode was experienced by one patient in each treatment group, while the incidence of edema was greater with rosiglitazone (4.1%) than vildagliptin (2.1%).

CONCLUSIONS — Vildagliptin is an effective and well-tolerated treatment option in patients with type 2 diabetes, demonstrating similar glycemic reductions as rosiglitazone but without weight gain.

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A promising new approach to treating type 2 diabetes is the augmentation of glucagon-like peptide (GLP)-1 receptor signaling by increasing endogenous GLP-1 through inhibition of the dipeptidyl peptidase IV (DPP-4) enzyme (1). Vildagliptin is a potent and selective DPP-4 inhibitor that improves islet function by increasing both α- and β-cell responsiveness to glucose (2,3). Vildagliptin has been shown in 12-week studies to decrease A1C when given as monotherapy (4,5) or in combination with metformin (6).

Head-to-head comparison studies recently have been recommended to better establish the efficacy and safety of investigational therapies, such as vildagliptin monotherapy, relative to other current therapies (7). Several classes of drugs are approved for the pharmacological treatment of type 2 diabetes, including the thiazolidinediones (TZDs), rosiglitazone, and pioglitazone, which are among the most recent additions to the therapeutic armamentarium. Accordingly, the present multicenter, 24-week, double-blind, randomized, controlled clinical trial was conducted to compare the efficacy and tolerability of monotherapy with vildagliptin (100 mg daily) versus rosiglitazone (8 mg daily) in drug-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— This was a 24-week, double-blind, randomized, active-controlled, parallel-group study conducted at 202 centers in 11 countries in the Americas and Europe. Eligible patients were randomized to receive vildagliptin 100 mg daily (given as equally divided doses) or rosiglitazone 8 mg daily (given as a once-daily dose) in a ratio of 2:1. Efficacy and tolerability were assessed at weeks 4, 12, 16, and 24 of active treatment.

The study enrolled type 2 diabetic patients with A1C in the range of 7.5–11.0%. These patients had received no pharmacologic treatment for at least 12

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Abbreviations: DPP-4, dipeptidyl peptidase IV; FPG, fasting plasma glucose; GLP, glucagon-like peptide; ITT, intention to treat; TZD, thiazolidinedione.

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

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weeks before screening and no antidiabetic agent for >3 consecutive months at any time in the past and were considered to be representative of a drug-naïve population. Male and female patients (nonfertile or of childbearing potential using a medically approved birth control method), aged 18–80 years, with BMI 22–45 kg/m^2 and with fasting plasma glucose (FPG) <15 mmol/l were eligible to participate.

Patients were excluded if they had a history of type 1 diabetes or secondary forms of diabetes; acute metabolic diabetes complications; myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months; congestive heart failure; liver disease, such as cirrhosis or chronic active hepatitis; and any contraindications and warnings according to the country-specific label for rosiglitazone. The following laboratory abnormalities were also excluded: alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal, direct bilirubin >1.3 times the upper limit of normal, serum creatinine levels >220 μmol/l, clinically significant abnormal thyroid-stimulating hormone, or fasting triglycerides >7.9 mmol/l.

A1C, FPG, body weight, and vital signs were measured at each study visit. Standard hematology and biochemistry laboratory assessments were made at each visit except on week 16. Fasting lipid profiles were measured and electrocardiograms were performed at screening and at weeks 0, 12, and 24.

All adverse events were recorded. Edema was assessed by the investigator as part of the normal adverse event–reporting process, either as a new occurrence or worsening of an existing condition. 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 a self-monitored blood glucose measurement <3.1 mmol/l plasma glucose equivalent. Severe hypoglycemia was defined as any episode requiring the assistance of another party.

All laboratory assessments were made by central laboratories. All assessments, except A1C, were performed by BARC (Bioanalytical Research Corporation). Assays were performed according to standardized and validated procedures in accordance with good laboratory practice. A1C measurements were performed by either BARC-EU (Ghent, Belgium) for European patients or by Diabetes Diagnostics Laboratory (Columbia, MO) or Covance-US (Indianapolis, IN) for patients from the Americas. All samples from any single patient were measured by the same laboratory.

Analysis populations and data analysis

The primary intention-to-treat (ITT) population consists of all randomized patients who *1*) had a screening A1C value ≥7.4%, *2*) received at least one dose of study medication, and *3*) had a baseline as well as at least one postbaseline A1C measurement. A total of 89 randomized patients were excluded from the primary ITT population for the following reasons: 4 received no intervention and 13 had no postbaseline A1C measurement; in addition, 61 patients were inappropriately randomized with screening A1C <7.4%, and 11 patients had no baseline A1C assessment due to a systematic error in the measurement of A1C by the U.S. laboratory originally used for the study. The U.S. laboratory was subsequently changed, and no measurements performed by the initial laboratory are used in the analyses. The statistical power of the study was preserved by recruitment of additional patients, and all samples from any single patient were measured by the same laboratory throughout the study. The safety population consists of all patients who received at least one dose of the study drug and had at least one postbaseline safety assessment.

The primary efficacy variable was the change from baseline in A1C at study end point using the last observation carried forward for patients who discontinued early. Secondary efficacy parameters included changes in FPG, fasting plasma lipids, and body weight. The efficacy analyses were performed with data from the primary ITT population, which was prespecified as the main efficacy population. Change from baseline in primary and secondary end points were analyzed using an ANCOVA model, with treatment and pooled center as the classification variables and baseline as the covariate. A test for the noninferiority of vildagliptin to rosiglitazone in A1C was carried out through a CI approach. Noninferiority for A1C was established if the upper limit of the 95% CI for the between-treatment difference in the adjusted mean change from baseline to end point obtained from the ANCOVA model did not exceed 0.4%. For the secondary efficacy variables, tests of superiority were conducted at the two-sided significance level of 0.05. In addition, prespecified subanalyses of A1C changes were conducted based on initial (baseline) A1C and on BMI category.

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 — A total of 786 patients were randomized, and 697 patients comprised the primary ITT population (459 patients randomized to receive vildagliptin 100 mg daily and 238 patients randomized to rosiglitazone 8 mg daily); 782 patients comprised the safety population. Figure 1 summarizes the disposition of patients from screening through study end point, and Table 1 reports the demographic and baseline metabolic characteristics of the patients in the primary ITT population. The groups were well balanced, with A1C averaging 8.7% and FPG averaging 10.3 mmol/l in both treatment groups. One-third of patients had an A1C >9%. Participants were predominantly Caucasian and obese (30% with BMI ≥35 kg/m^2), with a mean age of 54 years and mean disease duration of 2.4 years. More than 85% of all patients randomized to either treatment completed the 24-week study.

Efficacy

Figure 2*A* depicts the time-course of mean A1C during the 24-week treatment with vildagliptin 100 mg daily or rosiglitazone 8 mg daily. Baseline A1C values were identical in the two treatment groups (8.7 ± 0.1%). A1C decreased with vildagliptin treatment over the entire 24-week study period, with most of the reduction attained by week 12. Rosiglitazone treatment appeared to have a somewhat slower onset of effect, with nearly maximum reduction reached at week 16. In the primary ITT population, the adjusted mean change in A1C from baseline to study end point was −1.1 ± 0.1% ($P < 0.001$) in patients receiving vildagliptin ($n = 459$) and −1.3 ± 0.1% ($P < 0.001$) in patients receiving rosiglitazone ($n = 238$). Noninferiority of vilda-

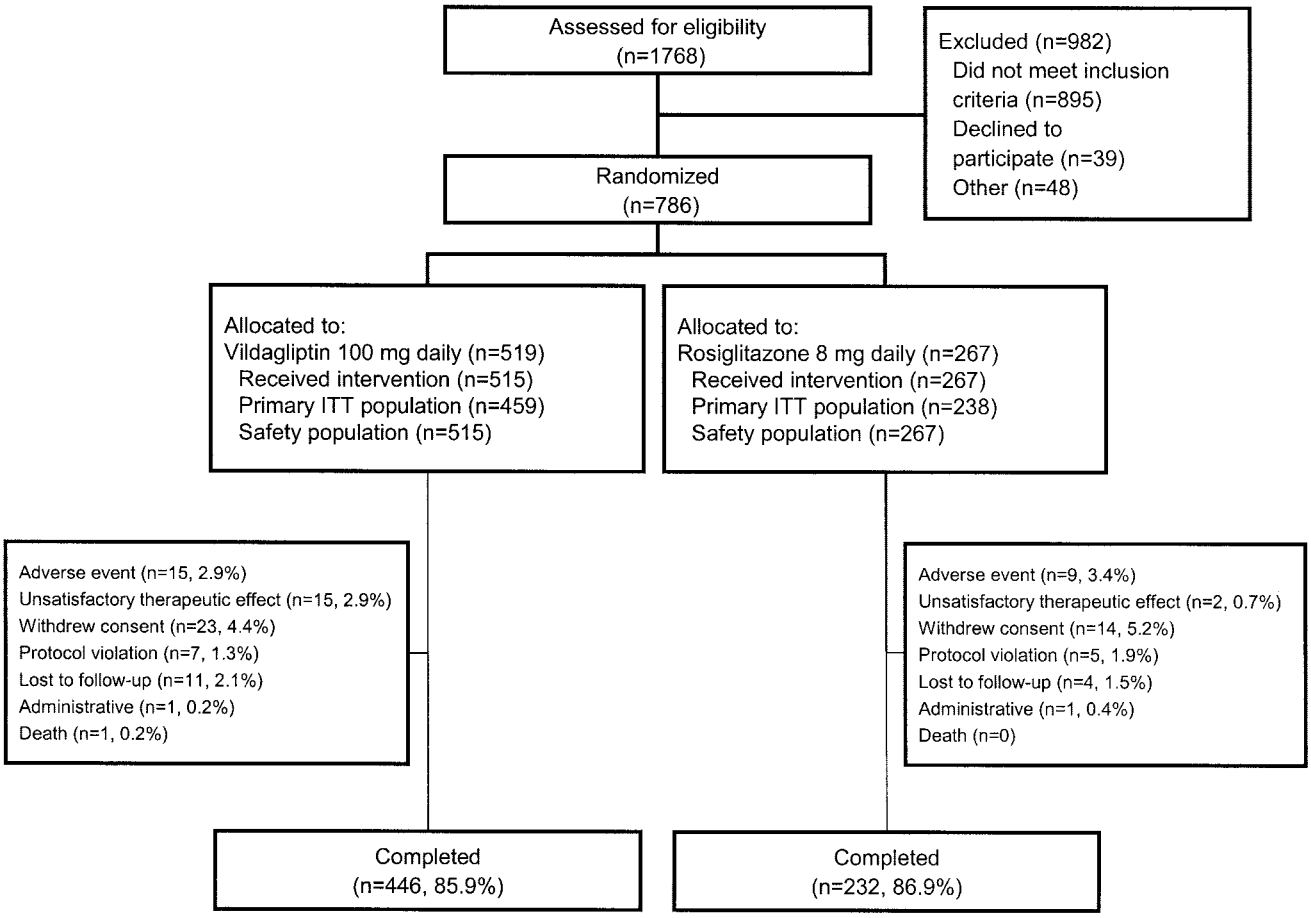

Figure 1— *Disposition of patients from screening through completion.*

gliptin 100 mg daily to rosiglitazone 8 mg daily was established, as the upper limit of the 95% CI for the between-group difference in adjusted mean change in A1C (−0.01 to 0.39) did not exceed the prespecified noninferiority margin.

The decrease in A1C with either agent was substantially larger in patients with baseline A1C >9.0%, with mean A1C reductions of −1.8 ± 0.1% ($P < 0.001$) from a baseline of 10.0% ($n = 166$) with vildagliptin and of −1.9 ± 0.2% ($P < 0.001$) from a baseline of 9.9% ($n = 88$) with rosiglitazone. In the vildagliptin group, patients with BMI <30 kg/m^2 showed a somewhat greater reduction in A1C (ΔA1C = −1.3 ± 0.1%, $n = 184$) compared with obese patients with BMI ≥30 kg/m^2 (ΔA1C = −1.0 ± 0.1%, $n = 275$). Rosiglitazone, on the other hand, was somewhat more efficacious in patients with BMI ≥30 kg/m^2 (ΔA1C = −1.4 ± 0.1%, $n = 155$) than in leaner patients (ΔA1C = −1.1 ± 0.2%, $n = 83$).

FPG also decreased significantly during the 24-week treatment with either

Table 1—*Baseline characteristics of the primary ITT population

	Vildagliptin 100 mg daily	Rosiglitazone 8 mg daily
n	459	238
Age (years)	54.5 ± 11.7	54.2 ± 11.6
Sex		
Male	264 (57.5)	137 (57.6)
Female	195 (42.5)	101 (42.4)
Race		
Caucasian	365 (79.5)	190 (79.8)
Hispanic or Latino	51 (11.1)	29 (12.2)
Black	27 (5.9)	11 (4.6)
All other	16 (3.5)	8 (3.4)
BMI (kg/m^2)	32.2 ± 5.7	32.9 ± 6.0
BMI group (kg/m^2)		
<30	184 (40.1)	83 (34.9)
≥30	275 (59.9)	155 (65.1)
≥35	132 (28.8)	76 (31.9)
A1C (%)	8.7 ± 1.1	8.7 ± 1.1
A1C group (%)		
≤9.0	293 (63.8)	150 (63.0)
>9.0	166 (36.2)	88 (37.0)
FPG (mmol/l)	10.3 ± 2.7	10.3 ± 2.9
Disease duration (years)	2.3 ± 3.4	2.7 ± 4.2

Data are means ± SD or *n* (%). *Baseline characteristics were similar in the randomized population.

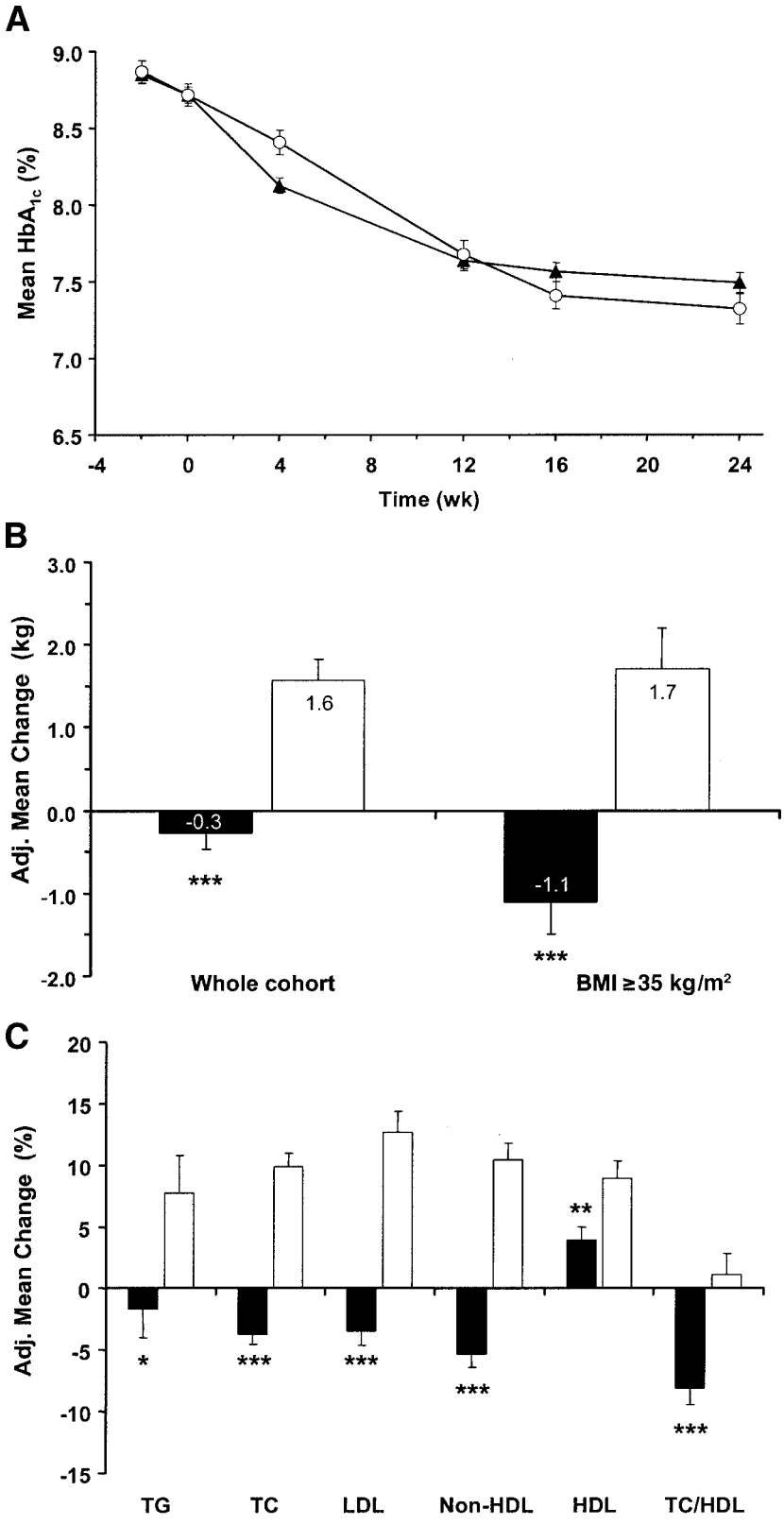

Figure 2—A: *Mean ± SE A1C during the 24-week treatment with vildagliptin (100 mg daily; ▲) or rosiglitazone (8 mg daily; ○) in patients with type 2 diabetes (primary ITT population: vildagliptin,* n *= 434 at week −2,* n *= 397 at week 24; rosiglitazone,* n *= 221 at week −2,* n *= 209 at week 24).* B: *Adjusted mean change from baseline to end point in body weight in the primary ITT population and in subgroup of patients with BMI ≥35 kg/m*^{2}. ■, *vildagliptin 100 mg daily;* □, *rosiglitazone 8 mg daily.* *P $<$ *0.05;* **P $<$ *0.01;* ***P $<$ *0.001 vs. rosiglitazone.* C: *Adjusted mean change from baseline to end point in fasting lipid parameters in the primary ITT population.* ■, *vildagliptin 100 mg daily;* □, *rosiglitazone 8 mg daily.* *P $<$ *0.05;* **P $<$ *0.01;* ***P $<$ *0.001 vs. rosiglitazone.*

agent. In the primary ITT population, the mean baseline FPG was 10.3 mmol/l in both treatment groups. The FPG reduction (adjusted mean change) was −1.3 ± 0.1 mmol/l ($P < 0.001$) in patients receiving vildagliptin and −2.3 ± 0.2 mmol/l ($P < 0.001$) in patients receiving rosiglitazone ($P < 0.001$ vs. vildagliptin).

Lipids and body weight

Figure 2 also depicts changes in body weight (*B*) and fasting lipid parameters (*C*) after the 24-week treatment with vildagliptin 100 mg daily or rosiglitazone 8 mg daily in the primary ITT population. Body weight at baseline averaged 91.2 ± 0.9 kg in the vildagliptin group and 93.1 ± 1.3 kg in the rosiglitazone group. Body weight did not change during 24-week treatment with vildagliptin but increased significantly during rosiglitazone monotherapy. The between-treatment difference in body weight was −1.9 ± 0.3 kg ($P < 0.001$). In addition, a post hoc analysis indicated that in the more severely obese population (BMI ≥35 kg/m^2; mean body weight of ~111 kg; n = 208), a larger decrease in body weight was seen with vildagliptin, while the increase seen with rosiglitazone monotherapy was similar to the overall cohort. The between-treatment difference in body weight in this subpopulation was −2.8 ± 0.6 kg ($P < 0.001$).

In the primary ITT population, fasting lipid levels were similar in the two treatment groups at baseline, averaging 2.3 mmol/l for triglycerides, 5.3 mmol/l for total cholesterol, 3.1 mmol/l for LDL, 1.2 mmol/l for HDL, and 4.1 mmol/l for non-HDL cholesterol in the combined cohort, with a total-to-HDL cholesterol ratio of 4.7. Relative to rosiglitazone, vildagliptin produced significant decreases in triglycerides (−9%, $P = 0.010$) and total (−14%, $P < 0.001$), LDL (−16%, $P < 0.001$), and non-HDL cholesterol (−16%, $P < 0.001$) but less improvement in HDL cholesterol (+4 vs. +9% from baseline, $P = 0.003$ for between-group difference). Relative to rosiglitazone, vildagliptin decreased total-to-HDL cholesterol by 9.1 ± 1.9% ($P < 0.0001$).

Tolerability

During the 24-week treatment, one or more adverse event was reported by 61.4% of patients receiving vildagliptin 100 mg daily and by 64.0% of patients receiving rosiglitazone 8 mg daily. In patients receiving vildagliptin, the most frequent specific adverse events (≥4% in either group) were nasopharyngitis (6.8%), dizziness (6.0%), headache (5.0%), and upper respiratory tract infection (4.5%). In rosiglitazone-treated patients, the most common adverse events were nasopharyngitis (7.5%), headache (5.2%), dizziness (4.1%), and peripheral edema (4.1%). The incidence of peripheral edema with vildagliptin was 2.1%. Increased body weight was reported as an adverse event in 0.8% of vildagliptin-treated patients and in 2.6% of rosiglitazone-treated patients. One patient in each group reported one mild hypoglycemic event, and no serious hypoglycemic events occurred in either group.

The proportion of patients experiencing any serious adverse event in the two treatment groups was comparable (2.9 vs. 3.0%), and no specific serious adverse event was reported by more than one patient within a treatment group. The frequency of discontinuations due to adverse events was also similar in the vildagliptin (2.9%) and the rosiglitazone (3.4%) groups. There was one death during the study. This was a 70-year-old male subject randomized to vildagliptin who died from postsurgical complications.

With the exception of a slightly higher proportion of patients with notable hematocrit and hemoglobin abnormalities in the rosiglitazone group, there were no major changes from baseline to end point nor were there any between-treatment differences observed for any laboratory parameter or vital signs. The frequency of treatment-emergent electrocardiogram abnormalities was low and comparable in the two treatment groups.

CONCLUSIONS — This study demonstrated that in patients representative of a drug-naïve population, vildagliptin was well tolerated and caused no weight gain despite a significant and clinically meaningful decrease from baseline in A1C that was similar to that with rosiglitazone. As expected, both vildagliptin and rosiglitazone produced more substantial reductions in A1C in the subgroup of patients with a high baseline level, and as in the whole cohort, the improvement in glycemic control was similar in patients with high baseline A1C receiving vildagliptin ($\Delta = -1.8\%$) or rosiglitazone ($\Delta = -1.9\%$). Vildagliptin appeared to be slightly more effective than rosiglitazone in patients with BMI <30 kg/m^2, and rosiglitazone was slightly more effective in obese patients (BMI ≥30 kg/m^2).

Although the two agents had similar overall efficacy to reduce A1C, the different mechanism of action of the two agents likely underlies several differences noted regarding secondary efficacy end points as well as in tolerability profiles. Vildagliptin inhibits the enzyme DPP-4, causing an increase in active plasma levels of the incretin hormones GLP-1 and gastrointestinal polypeptide (3). Vildagliptin has been shown to improve islet function by increasing the ability of both α- and β-cells to sense and respond appropriately to glucose (2,8). These effects are thought to be mediated by GLP-1 (9). In contrast, the TZDs target insulin resistance acting by activation of peroxisome proliferator–activated γ receptors, which results in enhanced peripheral and hepatic insulin action (10). Furthermore, TZDs stimulate differentiation of preadipocytes into new, small, and highly insulin-sensitive fat cells (10). This promotes storage of free fatty acids in adipose tissue, thus relieving the liver and muscle from lipotoxicity and reducing gluconeogenesis (11). The decrease in FPG in vildagliptin-treated patients seen in the present study was significantly less than that in patients receiving rosiglitazone, but the A1C improvements were similar, suggesting a more pronounced effect of vildagliptin on plasma glucose levels in the postprandial period and throughout the day.

Many effective antidiabetes agents lead to some weight gain as a result of improved glycemic control (12), and this is a particular limitation of (13) and potential safety concern about TZDs, due to their tendency to cause fluid retention and edema (14). In this study, the increase in body weight and incidence of edema in patients receiving rosiglitazone that was observed is consistent with previous reports, whereas vildagliptin achieved a comparable improvement in glycemic control with no weight gain and a low incidence of edema. The ability of vildagliptin to improve glycemic control without weight gain needs to be further clarified mechanistically.

In the present study, relative to rosiglitazone, vildagliptin treatment was associated with a significant improvement in triglycerides; total, LDL, and non-HDL cholesterol; and, importantly, the total-to-HDL cholesterol ratio. The changes in fasting lipids seen in rosiglitazone-treated patients were consistent with those re-

ported in previous studies (15–17). The mechanism underlying the improvement in lipid profile seen in vildagliptin-treated patients is unknown but could reflect a chronic improvement in postprandial lipids, as suggested by a recent report that found decreased postprandial lipemia primarily through a reduction in intestinally derived apolipoprotein B-48–containing particles after a 4-week treatment with vildagliptin (8).

With the exception of a higher incidence of edema in rosiglitazone-treated patients, the two agents were similarly well tolerated in this 24-week study of vildagliptin 100 mg daily versus rosiglitazone 8 mg daily, and there was a very low incidence of hypoglycemia.

In conclusion, similar A1C efficacy can be achieved using the DPP-4 inhibitor vildagliptin or a TZD as monotherapy in drug-naïve patients with type 2 diabetes. Vildagliptin is well tolerated, and, despite the improvement in glycemic control, it does not cause weight gain, which is an important consideration in the decision-making process for selecting first-line therapy in type 2 diabetes.

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APPENDIX

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ORIGINAL ARTICLE

Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea

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Aim: The broadly used combination of metformin and sulphonylurea (SU) often fails to bring patients to glycaemic goal. This study assessed the efficacy and safety of vildagliptin as add-on therapy to metformin plus glimepiride combination in patients with type 2 diabetes mellitus (T2DM) who had inadequate glycaemic control.

Methods: A multicentre, double-blind, placebo-controlled study randomized patients to receive treatment with vildagliptin 50 mg bid (n = 158) or placebo (n = 160) for 24 weeks.

Results: After 24 weeks, the adjusted mean change in haemoglobin A1c (HbA1c) was −1.01% with vildagliptin (baseline 8.75%) and −0.25% with placebo (baseline 8.80%), with a between-treatment difference of −0.76% ($p < 0.001$). Significantly more patients on vildagliptin achieved the HbA1c target <7% (28.3% vs. 5.6%; $p < 0.001$). The difference in fasting plasma glucose reduction between vildagliptin and placebo was −1.13 mmol/l ($p < 0.001$). In subgroup of patients with baseline HbA1c ≤8%, vildagliptin reduced HbA1c by 0.74% from baseline 7.82% (between-treatment difference: −0.97%; $p < 0.001$) with significantly more patients achieving the HbA1c target <7% (38.6% vs. 13.9%; $p = 0.014$). Vildagliptin was well tolerated with low incidence of hypoglycaemia, slightly higher than with placebo (5.1% vs. 1.9%) and no clinically relevant weight gain.

Conclusions: Vildagliptin significantly improved glycaemic control in patients with T2DM inadequately controlled with metformin plus glimepiride combination. The addition of vildagliptin was well tolerated with low risk of hypoglycaemia and weight gain. This makes vildagliptin an attractive treatment option for patients failing on metformin plus SU particularly in patients with baseline HbA1c ≤8%.

Keywords: DPP-4 inhibitor, glimepiride, metformin, oral antidiabetic drug, type 2 diabetes, vildagliptin

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease that often requires combination of antidiabetic drugs with different mechanisms of action to achieve glycaemic targets [1–3]. The broadly used combination of metformin and a sulphonylurea (SU) fails to maintain glycaemic control over time [4] and the addition of a third antihyperglycaemic agent is required.

When choosing options for the third agent, physicians should consider improvement of glycaemic control without additional risks such as hypoglycaemia and weight gain [5]. While insulin is recommended as a preferred next step by many international and local guidelines in patients failing on dual therapy [1–3], parenteral administration, increased risk of hypoglycaemia and weight gain may limit the use of insulin. Negative attitudes towards initiation of insulin and a preference for oral therapies by many patients should also be taken into account. Hence, a third oral agent that provides sustained glycaemic control and delays the time to permanent use of insulin could benefit patients who are reluctant to start injectable therapy [1,6].

Vildagliptin, a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), improves glycaemic control by increasing the availability of endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [7,8]. Complementing the pharmacological effect of metformin, vildagliptin enhances glucose-dependent insulin secretion and suppresses glucagon release, thereby improving glycaemic control, and contributing to weight-neutrality and reduced hypoglycaemia [9]. Vildagliptin has demonstrated similar efficacy as an add-on to metformin when compared to SU with markedly reduced hypoglycaemia risk and no weight gain [10,11].

This study evaluated the efficacy and safety of vildagliptin 50 mg bid as an add-on therapy in patients with T2DM inadequately controlled with dual therapy of metformin

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(≥1500 mg) and glimepiride (≥4 mg). Of particular interest was whether and which patient population could achieve glycaemic control with such a triple combination.

Methods

Study Design and Patients

This was a 24-week, multicentre, randomized, double-blind, placebo-controlled study in patients with T2DM. Eligible patients were 18–80 years of age, had body mass index (BMI) ≥22 to ≤45 kg/m^2, and were inadequately controlled on a stable dose of oral antidiabetic drugs (OADs) for at least 12 weeks prior to the screening visit. Acceptable background therapy prior to enrollment included metformin ≥1500 mg as monotherapy [haemoglobin A1c (HbA1c) ≥8.5 and ≤11%] or dual combination of metformin ≥1500 mg with SU, thiazolidinedione (TZD) or glinide (HbA1c ≥7.5 and ≤11%). Eligible patients continued their current metformin treatment ≥1500 mg throughout the study. Patients were excluded if they had fasting plasma glucose (FPG) ≥15.0 mmol/l; significant hepatic, renal or cardiovascular medical conditions; significant laboratory abnormalities; and pregnant or lactating females.

The study consisted of a 1–2 week screening period, an up to 12-week titration and/or stabilization period (depending on the type and dose of background OAD at study entry) and a 24-week double-blind treatment period. After screening, eligible patients who were (i) on metformin ≥1500 mg plus glimepiride ≥4 mg for at least 12 weeks proceeded directly to randomization; (ii) on metformin monotherapy ≥1500 mg entered a titration and stabilization period for glimepiride up to 4 mg; (iii) on any other combination with metformin discontinued their SU, TZD or glinide therapy, and entered titration and/or stabilization for glimepiride up to 4 mg. Patients were discontinued from the study if they could not tolerate the prescribed dose of metformin ≥1500 mg or glimepiride ≥4 mg during stabilization period. Eligible patients with HbA1c ≥7.5 and ≤11% at the end of stabilization period were randomized (1 : 1) to receive either vildagliptin 50 mg bid or placebo in addition to their metformin ≥1500 mg plus glimepiride ≥4 mg therapy for 24 weeks.

After randomization, the dose of metformin (≥1500 mg) was kept stable. The dose of glimepiride, however, could be adjusted downward for safety reasons at the investigators' discretion. Rescue medication (insulin or pioglitazone, per investigator discretion) was prescribed if the patient had FPG >13.3 mmol/l between week 6 and 12, FPG >11.1 mmol/l between week 12 and 24 or symptoms of worsening of hyperglycaemia at any visit.

Study Assessments and Endpoints

The primary endpoint was change in HbA1c from baseline to week 24 or to the final visit. Secondary efficacy assessments included change in FPG from baseline to week 24 endpoint and responder rates achieving HbA1c targets of <7 or ≤6.5%. Safety assessments included recording and monitoring of treatment-emergent adverse events (AEs); biochemistry and haematology laboratory test results; electrocardiogram (ECG) findings and vital signs. Hypoglycaemia was defined by symptoms suggestive of hypoglycaemia and a self-monitored plasma glucose measurement <3.1 mmol/l. Severe hypoglycaemia was defined as an episode that required assistance of another person or hospitalization with or without a plasma glucose measurement <3.1 mmol/l.

Statistical Analysis

A sample size of 246 completed patients (123 per arm) would ensure 90% power with a one-sided significance level of 2.5% to declare superiority of vildagliptin 50 mg bid over placebo in HbA1c reduction (%) from baseline after 24 weeks of treatment, assuming a clinically relevant difference of 0.5 absolute units between treatments and a standard deviation of 1.2%. Assuming a drop-out rate of 15%, about 290 patients (145 patients per arm) were to be randomized with an equal randomization ratio 1 : 1 to the two treatment groups.

The adjusted mean changes in HbA1c and FPG from baseline to week 24 were compared between vildagliptin and placebo using an analysis of covariance model with treatment and pooled centre as a classification factor and baseline HbA1c as a covariate. This comparison was performed on full analysis set (FAS) consisting of all randomized patients who received at least one dose of the study drug and had at least one post-randomization efficacy parameter measurement. In addition, responder rates (percentage of patients achieving endpoint HbA1c <7.0 or ≤6.5%) were compared between treatments using a chi-squared test.

Efficacy data used in the analyses were censored at the start of rescue medication. The last observation carried forward (LOCF) method was used to handle missing data because of early discontinuation or data censoring. Safety data were summarized descriptively by treatment. All data of patients who received at least one dose of study medication were included in analysis for safety assessment.

Ethical Statement

This trial was conducted in accordance with the Declaration of Helsinki. An independent ethics committee or institutional review board at each research site reviewed the study protocol. Each patient gave written informed consent before randomization.

Results

Patient Disposition and Baseline Characteristics

The disposition of patients from screening to study endpoint is depicted in figure 1. Of the 564 patients screened, 318 were randomized to vildagliptin (n = 158) and placebo (n = 160). The most common reason for screen failure was having not met the diagnostic/severity criteria (66.8%) and unacceptable laboratory values (55.7%). The percentage of randomized patients who discontinued the study was overall low and slightly higher in the vildagliptin group (8.9%) than in the placebo group (3.1%) mainly due to a greater percentage of patients who withdrew consent (4.4% vs. 1.3%, respectively).

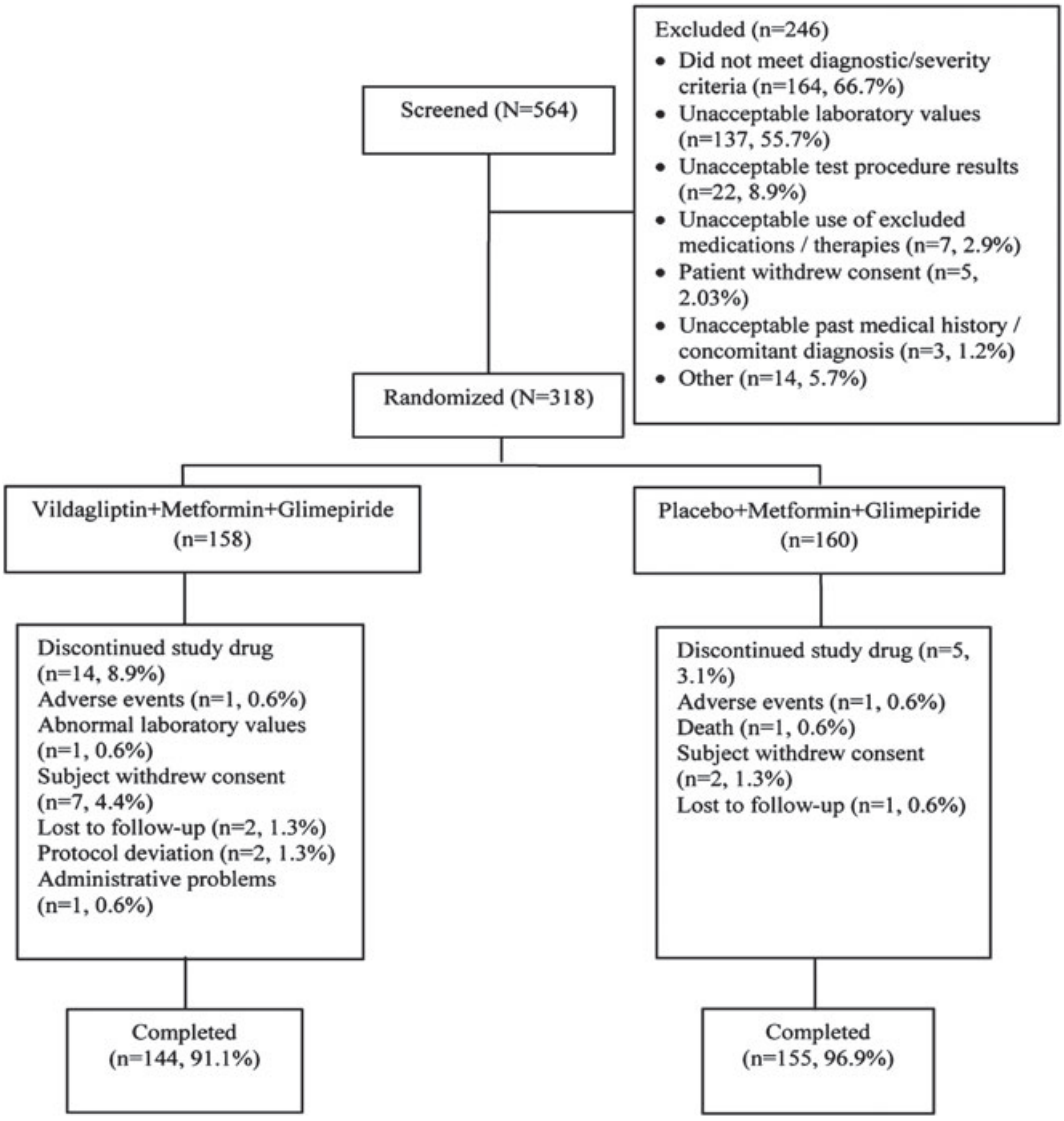

Figure 1. Patient disposition.

The demographic and baseline characteristics of the randomized patients were generally similar between the treatment groups (Table 1). The mean dose of metformin at screening was 1810 mg/day with 43.7% of patients receiving ≥2000 mg daily dose. Approximately 80% of patients (n = 254) were already treated with metformin plus glimepiride with a mean daily glimepiride dose of 4.4 mg; 35 of those patients who were on glimepiride <4 mg were up-titrated to 4 mg. Besides glimepiride, 59 (18.5%) patients were receiving other SUs, 1 (0.3%) patient was on a TZD and 4 (1.2%) patients were on metformin monotherapy at screening; all these patients were switched and up-titrated to glimepiride 4 mg as per protocol.

Efficacy

Vildagliptin had a sustained glucose-lowering effect during 24 weeks of treatment (figure 2A). The adjusted mean change in HbA1c at study end point in the vildagliptin group of −1.01% (baseline 8.75%) was significantly different from the 0.25% reduction in the placebo group (baseline 8.80%) with a between-treatment difference of −0.76% ($p < 0.001$) (figure 2B). Changes in HbA1c in subgroup analyses by baseline HbA1c, BMI, age, gender and race were in line with the overall study results.

After 24 weeks of treatment, a significantly higher percentage of patients on vildagliptin achieved HbA1c targets compared with placebo (HbA1c <7%: 28.3% vs. 5.6%, or HbA1c ≤6.5%: 13.2% vs. 1.3%, respectively; $p < 0.001$).

Vildagliptin demonstrated a clinically relevant reduction in FPG of 1.11 mmol/l (baseline 9.34 mmol/l) compared with nearly no change in the placebo group of +0.02 mmol/l (baseline 9.52 mmol/l). The difference versus placebo of −1.13 mmol/l was clinically and statistically significant ($p < 0.001$). Rescue medication was used by fewer patients in the vildagliptin group (n = 6/158, 3.8%) compared with the placebo group (n = 22/160, 13.8%).

Table 1. Patient baseline demographic and background characteristics (randomized set).

	Vildagliptin + Metformin + Glimepiride N = 158	Placebo + Metformin + Glimepiride N = 160	Total N = 318
Age, years	55.3 (10.2)	55.0 (11.1)	55.1 (10.6)
≥65, n (%)	29 (18.4)	38 (23.8)	67 (21.1)
Gender, female, n (%)	78 (49.4)	88 (55.0)	166 (52.2)
Race, n (%)			
Asian	116 (73.4)	116 (72.5)	232 (73.0)
Indian	81 (51.3)	77 (48.1)	158 (49.7)
Chinese	12 (7.6)	21 (13.1)	33 (10.4)
Caucasian	34 (21.5)	38 (23.8)	72 (22.6)
Other	8 (5.1)	6 (3.8)	14 (4.4)
BMI, kg/m^2	27.9 (4.6)	28.0 (4.5)	28.0 (4.5)
HbA1c, %	8.7 (0.9)	8.8 (0.9)	8.8 (0.9)
≤8%, n (%)	48 (30.4)	36 (22.5)	84 (26.4)
≤9%, n (%)	99 (62.7)	102 (63.8)	201 (63.2)
FPG, mmol/l	9.3 (2.4)	9.5 (2.1)	9.4 (2.3)
Duration of T2DM, years	7.1 (6.2)	7.5 (6.1)	7.3 (6.1)
GFR (MDRD), ml/min/1.73 m^2, n (%)			
Normal, >80	99 (62.7)	104 (65.0)	203 (63.8)
Mild, ≥50 to ≤80	55 (34.8)	50 (31.3)	105 (33.0)
Moderate, ≥30 to <50	4 (2.5)	6 (3.8)	10 (3.1)

Values are mean (s.d.) unless indicated otherwise. BMI, body mass index; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, haemoglobin A1c; MDRD, modification of diet in renal disease; T2DM, type 2 diabetes mellitus.

Table 2. Overall summary of adverse events (AEs) by treatment group (safety set).

Event	Vildagliptin + Metformin + Glimepiride N = 157, n (%)	Placebo + Metformin + Glimepiride N = 160, n (%)
AEs	79 (50.3)	76 (47.5)
SAEs	3 (1.9)	2 (1.3)
Discontinuation due to AEs	1 (0.6)	2 (1.3)
Deaths	0 (0.0)	1 (0.6)
Hypoglycaemic events	8 (5.1)	3 (1.9)
Severe hypoglycaemia	1 (0.6)	0 (0.0)
Discontinuation due to hypoglycaemia	0 (0.0)	0 (0.0)

In a subgroup of patients with baseline HbA1c ≤8% (n = 80, 44 patients on vildagliptin and 36 patients on placebo), vildagliptin provided a significant HbA1c reduction of 0.74% from baseline HbA1c 7.82% compared with an increase of 0.23% in the placebo group from baseline HbA1c 7.67%; the between-treatment difference was −0.97% ($p < 0.001$). The responder analysis demonstrated that significantly more patients receiving vildagliptin (38.6%) achieved an HbA1c target of <7.0% vs. placebo (13.9%) ($p = 0.014$) in this subgroup (figure 3).

Safety

The overall safety and tolerability of vildagliptin was similar to placebo when used in triple combination with metformin and SU (Table 2). The overall incidence of AEs was comparable between treatments, 50.3% vs. 47.5% in the vildagliptin and the placebo groups, respectively. Serious AEs and discontinuations due to AEs were similarly low in both treatment groups. There were no deaths in the vildagliptin group, one placebo-treated patient died due to suicide.

Urinary tract infection was the most frequent AE in both groups (vildagliptin: 6.4% and placebo: 8.1%). Slightly more vildagliptin-treated patients reported dizziness (7.0% vs. 1.9% with placebo) and hyperhidrosis (6.4% vs. 0.6% with placebo), which could be symptoms of hypoglycaemia.

The incidence of hypoglycaemia was overall low with both treatments; however, it was slightly higher in the vildagliptin group (n = 8, 5.1%) than in the placebo group (n = 3, 1.9%). Most of these patients had a single episode of hypoglycaemia; multiple hypoglycaemic events were only reported for one patient in each treatment group. The majority of the hypoglycaemic events were mild and none of them led to the discontinuation from the study. One patient in the vildagliptin group experienced a grade 2 hypoglycaemic event that was not study drug-suspected, but considered due to decreased food intake after a surgery.

No clinically relevant changes in the mean body weight from baseline to week 24 were observed: 73.1 kg at baseline vs. 73.6 kg at study endpoint in the vildagliptin group and 72.4 kg vs. 72.3 kg in the placebo group, respectively. There were no meaningful changes in laboratory values, physical examination results or ECGs between treatment groups. No patients receiving vildagliptin had a treatment emergent alanine aminotransferase or aspartate aminotransferase elevation ≥3x upper limit of normal.

Discussion

In this study, vildagliptin 50 mg bid added as a third OAD to a stable combination of metformin (≥1500 mg) and glimepiride

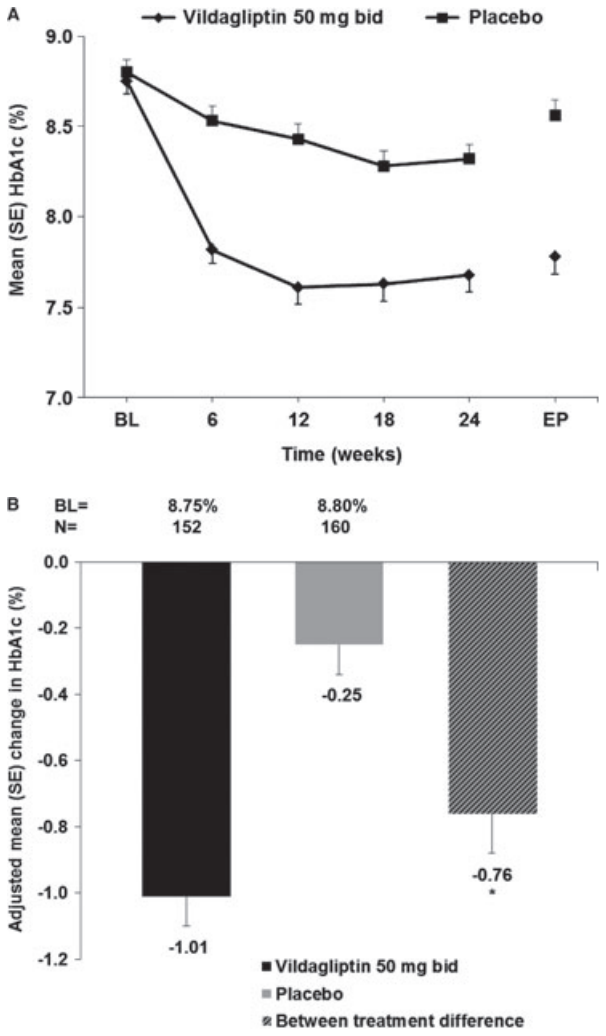

Figure 2. (A) Mean HbA1c (%) by treatment and visit (full analysis set). (B) Adjusted mean change in HbA1c from baseline to endpoint (full analysis set). BL, baseline; EP, endpoint; *$p < 0.001$.

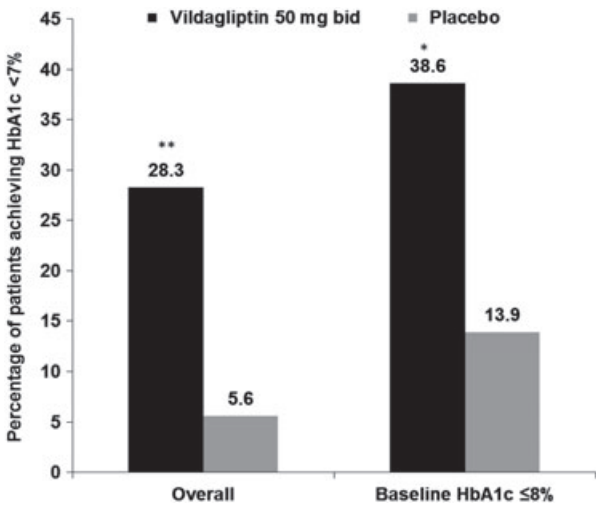

Figure 3. Proportion of patients achieving haemoglobin A1c (HbA1c) <7% with baseline ≥7% in overall population and in subgroup of patients with baseline HbA1c ≤8% (full analysis set). *$p = 0.014$; **$p < 0.001$.

(≥4 mg) provided a robust and clinically relevant reduction in HbA1c of 1.01% from a baseline of 8.75% in patients with T2DM not adequately controlled with dual therapy. The reduction in HbA1c observed in this study is similar to the reductions seen with vildagliptin when used in dual combination with metformin or SU from similar baseline [12,13]. About 30% of vildagliptin-treated patients (almost five-fold greater than in the placebo group) achieved HbA1c of <7% demonstrating that a significant proportion of patients who failed on broadly used dual combination could reach treatment target when vildagliptin was added as a third OAD. Other DPP-4 inhibitors have been studied as well in the combination with metformin and glimepiride. Both sitagliptin and linagliptin in combination with metformin and glimepiride decreased HbA1c by 0.6% compared with placebo from a similar baseline HbA1c of 8.3 and 8.2%, respectively [14,15], which appears slightly lower than the 0.8% difference versus placebo seen in our study.

Considerable uncertainty exists regarding optimal treatment for patients in whom glycaemic targets cannot be met with metformin and a SU in combination. Recent meta-analyses conducted to evaluate the benefits of the third antihyperglycaemic agent added to metformin and SU in patients with T2DM inadequately controlled on dual therapy demonstrated statistically significant reductions in HbA1c with different drug classes, including insulin (basal, biphasic and bolus), DPP-4 inhibitors, GLP-1 analogues and TZDs (−0.89 to −1.17%), but not with meglitinides and alpha-glucosidase inhibitors [5,16]. In light of relatively minor differences in terms of the glucose lowering efficacy between these drug classes, tolerability and absence of weight gain are key factors in the choice of the drug to be added to existing metformin plus SU therapy.

The addition of a third glucose lowering agent to existing dual therapy with metformin and SU has been associated with an increased risk of hypoglycaemia. This has been demonstrated for TZDs, and GLP-1 analogues. Insulin in triple combination even doubled the incidence of severe hypoglycaemic events [5,16]. Although DPP-4 inhibitors typically do not increase the risk of hypoglycaemia; in triple combination with metformin plus SU, sitagliptin and linagliptin reported more hypoglycaemic events than placebo, 16.4% versus 0.9% and 22.7% versus 14.8%, respectively. Thus, a slightly higher rate of hypoglycaemia with vildagliptin (5.1%) compared to placebo (1.9%) in our study is consistent with the experience with other DPP-4 inhibitors [14,15].

The risk of hypoglycaemia seen in this study slightly differs from the data recently reported with vildagliptin in combination with insulin. In patients with advanced T2DM not adequately controlled with metformin plus insulin, the addition of vildagliptin 50 mg bid provided robust reduction in HbA1c with an incidence of hypoglycaemia similar to placebo [17]. The generally low risk of hypoglycaemia in triple combinations might be due to vildagliptin's effect to increase GIP levels

between meals and overnight when hypoglycaemia is most likely to occur [18], thereby increasing glucagon levels in hypoglycaemia [19]. The slightly greater risk of hypoglycaemia versus placebo with vildagliptin added to metformin plus SU compared to similar incidence of hypoglycaemic events with vildagliptin in combination with metformin and insulin might be due to uncoupling of the glucose-dependent insulinotropic effect of GLP-1 in the presence of SU [20].

Consistent with other findings from the DPP-4 inhibitors [21–23] the glucose-lowering effect of vildagliptin was not associated with an increase in weight. In contrast, TZDs or insulin added to metformin plus SU have been associated with an increase in body weight [24,25].

Ultimately, the clinical objective of treatment intensification is to achieve glycaemic control in as many patients as possible. We were therefore interested which patient group might get closest to this goal and analysed the efficacy and safety in patients having baseline HbA1c $\leq$8%. The results showed that approximately 40% of patients receiving vildagliptin responded to treatment demonstrating the benefit of triple therapy for this subgroup.

One limitation of our study is its relatively short 24-week duration. Longer study will be required to assess the durability effect of vildagliptin in triple combination as well as its potential in delaying the time to permanent use of insulin. However, durable glycaemic control with vildagliptin as monotherapy has been demonstrated previously [26].

In conclusion, vildagliptin in triple combination with metformin and SU demonstrated robust glucose-lowering efficacy and good safety with low risk of hypoglycaemia and weight gain. This makes vildagliptin an attractive treatment option for patients with T2DM failing on metformin and SU who require a third antihyperglycaemic agent and are not candidates for an insulin therapy, especially in patients with baseline HbA1c $\leq$8% as a substantial number of patients in this subgroup achieved treatment targets.

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Conflict of Interest

V. L. was critical to designing and conducting the trial, data collection and initial data interpretation. M. A. was responsible for the statistical analysis. W. K. contributed to study design, the initial data interpretation and overall clinical interpretation. S. D. P. represented the study investigators and contributed to the clinical interpretation of the data. All authors were involved in manuscript revisions and are responsible for intellectual content. V. L., M. A. and W. K. are employed by and own shares in Novartis. S. D. P. has served on advisory boards, received honoraria for speaking engagements and received research support from Novartis.

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ORIGINAL ARTICLE

Improved glycaemic control with vildagliptin added to insulin, with or without metformin, in patients with type 2 diabetes mellitus

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Aim: The aim of this study is to assess the efficacy and safety of vildagliptin 50 mg bid as add-on therapy to insulin in type 2 diabetes mellitus (T2DM).

Methods: This is a multicentre, double-blind, placebo-controlled, parallel group, clinical trial in T2DM patients inadequately controlled by stable insulin therapy, with or without metformin. Patients received treatment with vildagliptin 50 mg bid or placebo for 24 weeks.

Results: In all, 449 patients were randomized to vildagliptin (n = 228) or placebo (n = 221). After 24 weeks, the difference in adjusted mean change in haemoglobin A1c (HbA1c) between vildagliptin and placebo was $-0.7 \pm 0.1\%$ ($p < 0.001$) in the overall study population, $-0.6 \pm 0.1\%$ ($p < 0.001$) in the subgroup also receiving metformin and $-0.8 \pm 0.2\%$ ($p < 0.001$) in the subgroup without metformin. Vildagliptin therapy was well tolerated and had a similarly low incidence of hypoglycaemia compared with placebo (8.4 vs. 7.2%, $p = 0.66$) in spite of improved glycaemic control, and was not associated with weight gain. (+0.1 vs. −0.4 kg).

Conclusions: Vildagliptin 50 mg bid added to insulin significantly reduced HbA1c in patients with T2DM inadequately controlled by insulin, with or without metformin. Vildagliptin was well tolerated, with a safety profile similar to placebo. These results were achieved without weight gain or an increase in hypoglycaemia incidence or severity in spite of improved glycaemic control.

Keywords: DPP-4 inhibitor, hypoglycaemia, insulin, oral antidiabetic drug, type 2 diabetes, vildagliptin

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Introduction

Vildagliptin is a potent and selective, orally administered inhibitor of dipeptidyl peptidase-4 (DPP-4). It improves glycaemic control in patients with type 2 diabetes (T2DM) by blocking the degradation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which extends their physiological effects, thereby increasing pancreatic α- and β-cell sensitivity to glucose [1–3]. While both GLP-1 and GIP enhance glucose-mediated insulin secretion, GLP-1 reduces glucagon levels during hyperglycaemia and GIP increases glucagon levels during hypoglycaemia [2,4]. This GIP effect is of high interest because it could translate clinically into a protective effect against hypoglycaemia.

The concomitant use of insulin and a DPP-4 inhibitor is becoming an integrative part of T2DM therapy. Recently, in a joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) this treatment regimen was included in the therapeutic algorithm for T2DM treatment [5].

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Fonseca et al. [6] reported that vildagliptin 50 mg bid added to insulin monotherapy in patients with T2DM reduced haemoglobin A1c (HbA1c) from 8.4% to 7.9% (0.3% placebo subtracted difference), with a significantly reduced risk of hypoglycaemia, even with slight and similar increases in the daily insulin dose in both treatment groups. The efficacy results, however, were confounded by significant short-acting insulin usage and high mean daily doses of insulin (82 units at baseline) suppressing endogenous insulin secretion.

We now report a 24-week trial to assess the efficacy and safety of vildagliptin in patients with T2DM, inadequately controlled by stable long-acting, intermediate-acting or premixed insulin, with or without concomitant metformin therapy. In contrast with the previous trial, this trial is considered to be more reflective of the current clinical practise of using predominantly basal and premixed insulin. The primary objective of this placebo-controlled trial was to assess the efficacy of vildagliptin 50 mg bid as add-on therapy to insulin. Secondary objectives were assessments of efficacy and safety in the subgroups with and without concomitant metformin use. Exploratory objectives included measures of pancreatic β cell function and insulin resistance and sensitivity.

Methods

Patients and Trial Design

This multicentre, double-blind, placebo-controlled, parallel group, 24-week clinical trial included patients with T2DM who were being treated with stable insulin doses ≤1 U/kg/day (long-acting, intermediate-acting or premixed) with or without stable concomitant metformin treatment (≥1500 mg or maximally tolerated dose) for at least 12 weeks. Eligible patients were 18–80 years of age and had HbA1c values ≥7.5% and ≤11% and fasting plasma glucose levels (FPG) <15 mmol/l. Patients were excluded if they had an acute metabolic condition (such as ketoacidosis), acute or chronic liver disease, a myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, stroke or transient ischaemic attack within the previous 6 months, unstable angina within the previous 3 months or a current heart failure diagnosis (New York Heart Association class III or IV).

After a 2-week screening period, patients were randomized using interactive response technology for treatment with vildagliptin 50 mg bid or matching placebo bid. Randomization was stratified by metformin use and type of insulin used (long-acting vs. intermediate acting/premixed).

Insulin doses had to be maintained within 10% of baseline during the trial unless insulin dose adjustments were required for safety reasons. Insulin therapy enhancement as rescue was administered if FPG was >15 mmol/l before the week 8 visit, >13 mmol/l at week 8 up to the week 12 visit and >11 mmol/l at the week 12 visit up to study end. Insulin type and regimen were at the investigator's discretion.

Efficacy and Safety Assessments

HbA1c and FPG were assessed at every visit, scheduled at 4-week intervals. The primary end point was the change in HbA1c from baseline to week 24 or to the final visit. Responder rates were assessed at end point using predefined HbA1c targets of <7%.

Standard (75 g glucose load) 2-h oral glucose tolerance tests (oGTT) were performed at baseline, week 12, and study end to assess insulin secretion and sensitivity. Patients did not take study medications, insulin or metformin on the mornings prior to the test. Plasma glucose, C-peptide and insulin levels were measured at fasting (time 0), and at 15, 30, 60, 90 and 120 min. These measurements were used to determine insulin secretion rate relative to glucose, insulin resistance using the homeostasis model assessment for insulin resistance (HOMA-IR) and insulin sensitivity by calculation of the oral glucose insulin sensitivity (OGIS) index [7,8].

Safety assessments included recording and monitoring of treatment-emergent adverse events (AEs), biochemistry and haematology laboratory test results, electrocardiogram (ECG) findings and vital signs. Hypoglycaemia was defined by symptoms suggestive of hypoglycaemia and a self-monitored plasma glucose measurement <3.1 mmol/l. Severe hypoglycaemia was defined as an episode that required assistance of another person or hospitalization with or without a plasma glucose measurement <3.1 mmol/l.

Statistical Analysis

The primary end point, the change from baseline in HbA1c at week 24, was compared between vildagliptin and placebo using an analysis of covariance with treatment, region, metformin use and insulin type as classification variables, and baseline HbA1c as a covariate. This comparison was performed on the full analysis Set (FAS – including all randomised patients who received at least one dose of study drug and had at least one postbaseline efficacy measurement) as well as the two subgroups of patients with/without concomitant metformin within FAS. Other efficacy variables (FPG, HOMA-IR and OGIS) were analysed using similar models as for the primary end point. In addition, responder rates were compared between treatments using a chi-squared test.

Efficacy data used in the analysis were censored at the start of major changes in insulin therapy. Major changes in insulin therapy were defined as changes occurring ≥7 days in any 30-day period or ≥5 days consecutively, including changes in insulin frequency and/or type and/or a ≥10% dose increase either as rescue medication or for any other reasons. The last observation carried forward (LOCF) method was used to handle missing data because of early discontinuation or data censoring.

Safety data were summarized descriptively by treatment. Hypoglycaemic incidences were compared between treatments using a chi-squared test. All available data were included in analysis for safety assessment.

Ethics Statement

This trial was conducted in accordance with the Declaration of Helsinki. An independent ethics committee or institutional review board at each research site reviewed the study protocol. Each patient gave written informed consent before randomization.

Results

Patient Disposition, and Demographic and Baseline Characteristics

This trial was conducted in Europe, Asia, Australia and Central America. A total of 449 patients were randomized: 228 patients to vildagliptin 50 mg bid and 221 patients to placebo. Overall, 61.5% was treated with metformin. Patients who discontinued included 8.8% in the vildagliptin group and 13.6% in the placebo group. The most common reasons for discontinuation were withdrawal of consent (vildagliptin 3.5% and placebo 5.4%) and AEs (vildagliptin 3.9% and placebo 1.8%).

Baseline demographics and characteristics were similar among groups (Table 1). Patients were predominately White or Asian with a mean age of 59 years; 30% was ≥65 years of age. Mean baseline values of HbA1c and FPG were 8.8% and 9.3 mmol/l. The mean duration of T2DM was 13 years with a mean duration of insulin usage of 4.4 years and a mean daily insulin dose at screening of 41 units. A majority of patients were taking antihypertensive medication (67% and 69% of patients in the vildagliptin and placebo groups, respectively)

Table 1. Baseline patient demographic and background characteristics and therapies.

	Vildagliptin 50 mg bid n = 228	Placebo n = 221
Age (year)	59.3 (9.9)	59.1 (10.1)
≥65 years, n (%)	68 (29.8)	67 (30.3)
Gender, female, n (%)	119 (52.2)	106 (48.0)
Race, n (%)		
White	116 (50.9)	116 (52.5)
Asian	87 (38.2)	86 (38.9)
Other	25 (11.0)	19 (8.6)
BMI (kg/m^2)	28.9 (4.4)	29.0 (4.6)
Weight (kg)	77.9 (16.2)	78.9 (16.7)
HbA1c (%)	8.8 (1.0)	8.8 (1.0)
FPG (mmol/l)	9.6 (2.6)	9.1 (2.5)
T2DM duration (year)	12.9 (6.9)	13.2 (7.9)
eGFR*	77.6	82.2
Insulin use at screening, n (%)		
Intermediate-acting	39 (17.1)	35 (15.8)
Long-acting	52 (22.8)	51 (23.1)
Premixed	137 (60.1)	135 (61.1)
Duration of insulin use (year)	4.4 (4.8)	4.5 (5.0)
Daily dose of insulin (IU)	39.9 (18.1)	41.9 (20.4)
Insulin injections/day	1.8 (0.4)	1.8 (0.4)
Metformin use at screening, n (%)		
Yes	139 (61.0)	137 (62.0)
No	89 (39.0)	84 (38.0)
Duration of metformin use (year)	6.7 (5.6)	7.8 (6.1)
Daily dose of metformin (mg)	1928 (511)	1948 (463)

Values are mean (s.d.) unless indicated otherwise. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose level; HbA1c, haemoglobin A1c; T2DM, type 2 diabetes mellitus.
*GFR (ml/min/1.73 m^2) was estimated using the MDRD formula.

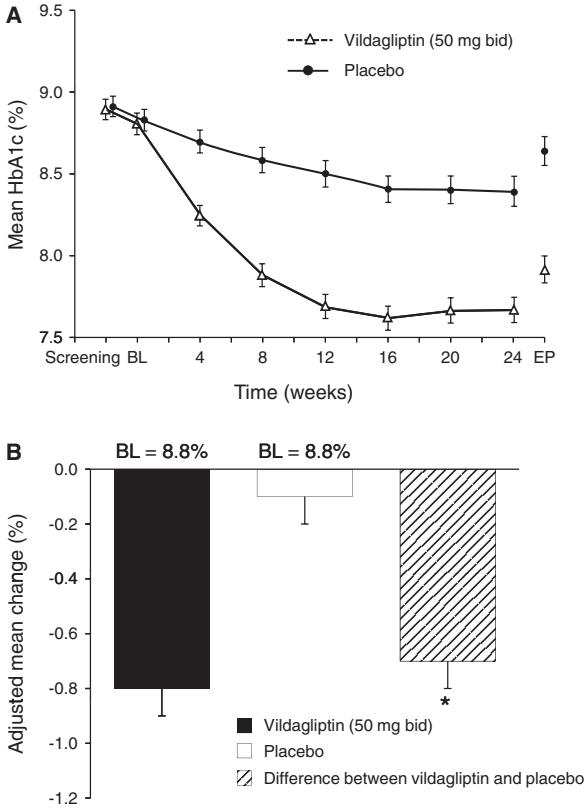

Figure 1. (A) Unadjusted mean changes (±s.e.) in HbA1c over time. (B) Adjusted mean change (±s.e.) in HbA1c from baseline to study end point. Study end point defined as the final available postrandomization assessment obtained at any visit, prior to start of major changes in insulin background therapy, up to the final scheduled visit including week 24. BL, baseline; EP, end point; *$p < 0.001$.

and approximately half were taking lipid-lowering medication (mostly statins).

Efficacy

The overall mean change (±s.e.) in HbA1c from a baseline of 8.8% to end point in the vildagliptin group was −0.8 ± 0.1%, which was significantly different from the −0.1 ± 0.1% reduction in the placebo group (figure 1); the difference vs. placebo was −0.7 ± 0.1% ($p < 0.001$). Vildagliptin significantly ($p < 0.001$) reduced HbA1c in both with and without concomitant metformin groups, with mean differences vs. placebo of −0.6 ± 0.1% and −0.8 ± 0.2%, respectively. Patients with higher HbA1c values (>8%) had greater reductions in HbA1c (−1.1% and −0.3% in the vildagliptin and placebo groups, respectively). The results by insulin type showed significant reductions with vildagliptin for all types of insulin used.

Significantly more patients receiving vildagliptin (22.2%) achieved the HbA1c target of <7% than those receiving placebo (5.1%; $p < 0.001$). Similar results for responder rates were shown in subgroups with or without metformin use.

Patients who received vildagliptin also had a greater reduction in FPG from a baseline of approximately 9.3 mmol/l (−0.8 mmol/l in the vildagliptin group and −0.2 mmol/l in the placebo group; mean placebo-subtracted difference of 0.6 mmol/l, $p = 0.050$). The mean difference between vildagliptin and placebo was greater in the subgroup not receiving concomitant metformin (−1.1 mmol/l) than in the groups receiving metformin (−0.2 mmol/l).

The mean insulin dose at baseline was 40.0 units in the vildagliptin and 42.1 units in the placebo group, and changed little in both treatment groups. The mean change from baseline to study end was −1.10 U in the vildagliptin group and −0.19 U in the placebo group. The percentage of patients who took rescue medication was slightly less in the vildagliptin group (10.1%) than in the placebo group (13.1%).

Mean changes from baseline to end point in insulin resistance (HOMA-IR) were not significantly different between groups overall (−0.7% and +3.2% change in the vildagliptin and placebo groups, respectively) or between groups receiving and not receiving metformin. Increases in the OGIS index were also small (+16.4 and +14.3, respectively) and not significantly different between treatment groups. Mean increases from baseline in fasting insulin were less in the vildagliptin group (8.3 pmol/l) than in the placebo group (18.8 pmol/l), but the difference was not statistically significant. However, the mean increase in insulin secretion rate relative to glucose during the oGTT was significantly higher in the vildagliptin group (n = 167) (+2.92 ± 0.48 pmol/m^2/min/mM) than in the placebo group

Table 2. Overall summary of adverse events (AEs) by treatment group.

	Vildagliptin 50 mg bid n = 227 n (%)	Placebo n = 221 n (%)
AEs	131 (57.7)	105 (47.5)
Serious AEs	9 (4.0)	9 (4.1)
AEs leading to discontinuation	9 (4.0)	5 (2.3)
Deaths	0	1 (0.5)

(n = 144; +0.26 ± 0.48 pmol/m^2/min/mM). The mean difference between groups was +2.65 ± 0.56 pmol/m2/min/mM ($p < 0.001$). The results in patients receiving or not receiving concomitant metformin were comparable.

Safety

The overall safety and tolerability of vildagliptin 50 mg added to intermediate-acting, long-acting or premixed insulin, with or without metformin, were generally comparable with placebo (Table 2). A slightly higher incidence of AEs was reported with vildagliptin (57.7%) than with placebo (47.5%), primarily because of more patients with infections and infestations (22.5%) and gastrointestinal disorders (13.7%) in the vildagliptin group than in the placebo group (14.5 and 7.2%, respectively) which reached statistical significance at the $p < 0.05$ level. All infections were judged by investigators to be mild/moderate and unrelated to study drug; the imbalance between vildagliptin and placebo was driven to a large extent by upper respiratory tract infections. The imbalance in gastrointestinal disorders was driven by diarrhoea, which only resulted in treatment discontinuation in one patient on vildagliptin. Cardiac events were infrequent with similar incidences for both treatment groups (4.4% on vildagliptin vs. 3.6% on placebo). Few patients in both groups had serious AEs, with no relevant between-group difference. Also, few and comparable percentages of patients had AEs that led to discontinuation. Diabetic ketoacidosis was the cause of death in one patient in the placebo group. Similar numbers of patients in the vildagliptin and placebo groups reported the most common AEs: hyperhidrosis (11.5% vs. 12.7%), dizziness (7.9% vs. 8.6%) and tremor (7% vs. 5%); these events could be manifestations of hypoglycaemia. Few patients experienced hypoglycaemic events (8.4% and 7.2% in the vildagliptin and placebo groups, respectively, $p = 0.66$) and the difference was not statistically significant. Most of the hypoglycaemic events were assessed as mild (90.2% and 94.4% in the vildagliptin and placebo groups, respectively). Severe hypoglycaemia was infrequent (two patients in each group). Among patients who received metformin, hypoglycaemia rates were similar (7.2% vs. 8.0% of patients for vildagliptin and placebo), without metformin, the percentages were 10.1% vs. 6.0%.

Body weights remained unchanged during the study with mean weight changes of 0.1 kg in the vildagliptin group and −0.4 kg in the placebo group. No clinically important changes in laboratory values, physical examination results, ECGs or vital signs were observed. One patient on vildagliptin reported an alanine aminotransferase increase of 342 U/l which was associated with respiratory infection. The hepatic enzymes normalized after the infection resolved, study drug had been discontinued as required by the protocol. Estimated glomerular filtration rate (eGFR) remained virtually unchanged (−2.8 ml/min/1.73 m^2 for vildagliptin and −2.2 ml/min/1.73 m^2 for placebo) and no patient experienced treatment emergent creatinine increases >2 mg/dl. Overall, the safety profile of vildagliptin in the subgroups with or without metformin was consistent with the safety profile in the overall patient population, without any notable differences between treatments.

Discussion

The key finding of this trial is that treatment with vildagliptin 50 mg bid in patients with T2DM inadequately controlled with basal or premixed insulin results in clinically and statistically improved glycaemic control without increased risk of hypoglycaemia. This was seen in patients with or without concomitant metformin use. Vildagliptin was well-tolerated and safe, with no increase in body weight, consistent with the safety profile derived from previous trials [9].

Our results are consistent with data from a recently published paper in patients with T2DM with moderate to severe renal impairment (RI). In this study, vildagliptin 50 mg qd significantly reduced HbA1c in these patients [10]. This reduction was achieved without an increased risk of hypoglycaemia. RI is common in T2DM patients, and insulin is the cornerstone of antiglycaemic therapy in these patients, with approximately 80% insulin use in patients with severe RI in the above mentioned study.

The HbA1c reduction with vildagliptin in the current trial was greater than the 0.5% drop from baseline observed by Fonseca et al. [6] when vildagliptin was added to insulin monotherapy. In that trial, patients were using daily insulin doses twice as high compared with the current trial, and were injecting insulin a mean of three times per day, which may have reduced the effects of vildagliptin on insulin secretion. Nevertheless, the HbA1c reductions were sustained with vildagliptin 50 mg/day in a 1-year extension [11]. Interestingly, the risk of hypoglycaemic events in the Fonseca study was reduced with vildagliptin therapy compared with placebo although glycaemic control was improved with vildagliptin.

In this study, we saw similar rates of hypoglycaemia for vildagliptin and placebo in spite of lower glucose levels with vildagliptin as reflected by the 0.7% lower HbA1c at end of study. Only two patients in each group experienced severe events in this trial. Taken together these studies indicate that vildagliptin reduces glucose levels when added to insulin therapy without increasing hypoglycaemia. From a clinician's perspective this is particularly relevant because hypoglycaemia negatively affects glycaemic control and patient compliance in patients with advanced diabetes who need insulin therapy [12]. The hypoglycaemia data discussed above actually suggest a reduced risk of hypoglycaemia at a given level of glycaemia, even in patients who have less β cell function. This result is consistent with GIP's effect to increase glucagon in hypoglycaemia [4], and with vildagliptin's effect to increase GIP levels between meal

and overnight when hypoglycaemia is most likely to occur [3]. A recent report indicates that this is also true in patients with type 1 diabetes [13].

Vildagliptin therapy in this study lowered HbA1 by 0.7% vs. placebo from a baseline of 8.8%. Other DPP-4 inhibitors also have been studied in combination with insulin therapy in a similar diabetic population. Alogliptin 12.5 mg and 25 mg decreased HbA1c from a somewhat higher baseline of 9.3% by 0.5% and 0.6% compared with placebo [14]. Sitagliptin 100 mg qd added to insulin with or without metformin reduced HbA1c by 0.6% vs. placebo from a baseline HbA1c of 8.7%, although this came with a doubling of hypoglycaemic risk [15]. Saxagliptin reported a relatively modest 0.4% drop against placebo also from a baseline of 8.7% [16]. These data indicate that all these DPP-4 inhibitors lower HbA1c in combination with insulin, and that slight differences between the clinical profiles may exist.

Vildagliptin also reduced FPG with a borderline significant difference vs. placebo ($p = 0.05$). It has been showed that concomitant insulin therapy already lowers FPG which may blunt the vildagliptin effect on FPG [17]. Therefore, it is likely that the HbA1c reduction seen in this study is predominantly driven by a reduction in post-prandial glucose as shown in previous vildagliptin studies [18]. This could be clinically important because improvements in postprandial glucose due to DPP4 inhibitor therapy might contribute to a potential cardiovascular benefit [19]. The significant improvement in β-cell function during the oGTT at end point in the vildagliptin group compared with placebo suggests that the robust reduction in HbA1c was at least partly because of enhanced β-cell secretion of insulin. As the patients did not take any antidiabetic medication before the test, the results indicate that ongoing treatment with vildagliptin for up to 24 weeks can improve the response of the β cell after a glucose load as a chronic effect. We did not measure glucagon in our study. However, considering the mode of action of vildagliptin, we can speculate that, in patients treated with insulin, both postprandial and fasting glucose levels can be improved by reducing both elevated postprandial and night-time glucagon levels in parallel with an enhancement of β-cell function as has been shown in patients not receiving insulin therapy [3].

Overall, vildagliptin was well tolerated in this study. A slightly higher incidence of AEs was seen with vildagliptin (57.7%) compared with the placebo group (47.5%), primarily driven by a higher rate of upper respiratory tract infections and diarrhoea. These events were generally assessed as mild or moderate and not suspected to the study drug by the investigator, and may not be related to study drug. Of note, in a pooled analysis of >6000 vildagliptin-treated patients, the rates of upper respiratory tract infections and gastrointestinal disorders events were similar for vildagliptin and comparators [9], and a meta-analysis of the vildagliptin clinical database did not find an increased risk of infections with vildagliptin in general [20].

In conclusion, vildagliptin 50 mg bid added to insulin significantly reduced HbA1c in patients with T2DM, who previously had inadequate glycaemic control with insulin with or without concomitant metformin therapy. Vildagliptin was well tolerated and these results were achieved without weight gain or significant effects on hypoglycaemia incidence or severity.

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Conflict of Interest

W. K. drafted the manuscript and contributed to study design, initial data interpretation and overall clinical interpretation. V. L. and P. K. were critical to designing and conducting the trial, data collection and initial data interpretation. Q. S. was responsible for the statistical analysis. J. F. contributed to the overall data interpretation and was involved in drafting the manuscript. B. G. represented the study investigators and contributed to the clinical interpretation of the data. All authors were involved in manuscript revisions and are responsible for intellectual content.

W. K., Q. S., J. F., P. K. and V. L. are employed by and have own shares in Novartis. B. G. has been a consultant for, and received honoraria for these activities as well as for lectures from, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Merck, Roche, Sanofi and Takeda.

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Clinical Safety and Tolerability of Vildagliptin – Insights from Randomised Trials, Observational Studies and Post-marketing Surveillance

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Vildagliptin is one of the most extensively studied dipeptidyl peptidase-4 (DPP-4) inhibitors in terms of its clinical utility. Over the last decade, a vast panorama of evidence on the benefit–risk profile of vildagliptin has been generated in patients with type 2 diabetes mellitus (T2DM). In this article, we review the cumulative evidence on the safety of vildagliptin from the clinical development programme, as well as reports of rare adverse drug reactions detected during the post-marketing surveillance of the drug. Across clinical studies, the overall safety and tolerability profile of vildagliptin was similar to placebo, and it was supported by real-world data in a broad population of patients with T2DM, making DPP-4 inhibitors, like vildagliptin, a safe option for managing patients with T2DM.

Keywords

Dipeptidyl peptidase-4 (DPP-4) inhibitors, post-marketing surveillance, safety, vildagliptin

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The introduction of vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, for the treatment of type 2 diabetes mellitus (T2DM) in 2007 provided clinicians with a novel and effective treatment option for lowering blood glucose, which neither caused weight gain nor increased the risk of hypoglycaemia.[1,2] However, looking back on early development, there were theoretical apprehensions regarding the overall benefit–risk profile of DPP-4 inhibitors as anti-diabetes agents, due to the involvement of DPP-4 in the metabolism of other bioactive peptides.[3] Being the first molecules under development, extensive *in vitro* and pre-clinical studies were conducted with vildagliptin and its predecessor, DPP-728, to map their off-target pharmacology. The *in vitro* and pre-clinical safety profiles were encouraging, with only a few species-specific safety signals pertaining to the gastrointestinal, cardiovascular (CV) and immune systems at concentrations that were approximately five to seven times the anticipated human exposure.[4,5] These insights from the pre-clinical studies were taken into account while designing the clinical development programme, and a special feature was the prospective, independent adjudication of CV events enabling a proper meta-analysis to establish the CV safety of vildagliptin at programme completion.

The benefit–risk profile of a new agent is seldom complete at the time of launch, as limited exposure in randomised controlled trials (RCTs) does not provide adequate evidence regarding the safety of the agent under real-world conditions.[6,7] It is therefore important to continuously monitor the safety of any therapeutic agent post-launch using a variety of complementary approaches. The concept of risk management, although used empirically, was formally introduced for all new medical entities in Europe in 2006.[8] This coincided with the time when the first DPP-4 inhibitors were approved. The main focus of a risk management plan (RMP) is to identify and minimise the risks associated with the drug. The use of RMPs, along with an increased emphasis on CV safety[9,10] led to the enrichment of the drug development programmes in diabetes, involving pooled safety analyses, meta-analyses and, when required, large, randomised, controlled outcome trials. These modalities, along with the real-world studies, paint the full picture of the safety, tolerability, and effectiveness of this class.

Vildagliptin, one of the earlier launched DPP-4 inhibitors,[11] is marketed in over 125 countries, and more than 17 million patients have been exposed to vildagliptin since its launch in 2007. This article reviews the overall safety and tolerability profile of vildagliptin, with a focus on adverse events (AEs) that have been of interest for patients with T2DM or for the DPP-4 inhibitor class in general. In addition to the pre-clinical data generated over the last decades, this article includes data from the latest vildagliptin CV meta-analysis,[12] observational studies,[13] findings from post-marketing surveillance (PMS) reported to the health authorities and the most recent cumulative safety analysis part of the periodic safety update report. The latter includes 58 phase II to IV Novartis-sponsored RCTs comprising more than 10,000 patients treated with vildagliptin 50 mg (once daily [qd]/ twice daily [bid]) and more than 8,000 patients treated with comparators (placebo and active comparators). AEs in all the studies were assessed by the investigator and were encoded using the MedDRA system. Mantel-Haenszel risk ratios (MHRR) were used to compare selected AEs between vildagliptin and comparators. The methodology for pooling and analysis is similar to that reported in the earlier pooled safety publications,[14,15] and results are expressed as exposure-adjusted incidence, i.e., number of patients having event over 100 subject-years of exposure (SYEs).

General safety and tolerability

Upon oral administration, vildagliptin is rapidly absorbed and is primarily eliminated by hydrolysis via multiple organs/tissues.[16] The diverse, non-cytochrome P450 (CYP)-mediated metabolic pathways and negligible protein binding (<10%) indicate a low potential for drug interactions for vildagliptin.[16] This was further confirmed in the drug interaction studies with commonly co-prescribed medications (metformin, pioglitazone, glyburide, simvastatin, amlodipine, valsartan, ramipril, digoxin and warfarin), which did not indicate any clinically relevant changes in the pharmacokinetics (PK) of any of the administered drugs.[17] Furthermore, the PK of vildagliptin is not affected by age, gender, body mass index, food or ethnicity.[18]

A wealth of evidence from RCTs and real-world studies has consistently demonstrated that vildagliptin is an effective and well-tolerated treatment, with an established weight neutrality and low risk of hypoglycaemia.[19,20] A pooled safety analysis of 58 trials (vildagliptin, n=10,331; 9,602 SYEs; all comparators, n=8,068; 7,386 SYEs) has shown that the frequency of overall AEs (64.5% versus 66.0% for vildagliptin versus all comparators, respectively), serious adverse events (SAEs; 8.0% versus 8.5%, respectively), discontinuations (5.2% versus 5.8%, respectively) and deaths (0.5% in both the groups) was similar between vildagliptin and all comparators. There was no specific trend in the AE and SAE profiles and the events were distributed across many different system organ classes (SOC). Similarly, no major imbalances were found between vildagliptin and comparators in the frequency of AEs leading to discontinuations. These findings are also supported by the large, real-life, Effectiveness of Diabetes control with vildaGliptin and vildagliptin/ mEtformin (EDGE) study (n=45868), in which the incidence of overall AEs was similar in the vildagliptin (5.3%) and comparator groups (5.7%).[13] Further evidence comes from a systematic review and meta-analysis, which concluded that vildagliptin is a safe therapeutic option for patients with T2DM, both as monotherapy and as add-on treatment.[19] Vildagliptin is approved for use as monotherapy and in combination with other anti-hyperglycaemic agents. It is also indicated for special populations (elderly, renal impairment) and there are no contraindications beyond hypersensitivity to the active constituent.[5] Overall, the evidence from RCTs and real-world studies provides reassurance regarding the general safety of vildagliptin in a broad population of patients with T2DM.[21]

Adverse events of special interest for dipeptidyl peptidase-4 inhibition-based therapies

Immune related and infections

DPP-4, also known as CD26, plays an essential role in immune response as it is extensively expressed on T-lymphocytes.[22] The DPP-4 catalytic site is a small part of CD26, and *in vitro* studies have shown that binding to the catalytic site does not affect binding on other sites of CD26. Concerted efforts were made in both early pre-clinical and clinical studies to identify any potential effects of vildagliptin on the immune system. In rats, vildagliptin was well tolerated at a daily dose of up to 900 mg/kg, and both primary and secondary immunoglobulin responses were not affected. Other animal studies have also confirmed that vildagliptin does not impair key parameters of the innate and adaptive immune responses.[23]

Similarly, data from clinical trials did not indicate an increased risk of infections, even in the most vulnerable subjects, such as very elderly or those with renal impairment.[24,25] In the pooled safety analysis, the overall exposure-adjusted incidence of AEs in the infections and infestations SOC was comparable between vildagliptin (33.1/100 SYEs) and all comparators (32.9/100 SYEs), and the incidence of SAEs in the same SOC was 1.5/100 SYEs in both the groups. Furthermore, in a comprehensive systematic review and meta-analysis, no increase in nasopharyngitis (odds ratio [OR] 1.06; 95% confidence interval [CI] 0.93–1.21), upper respiratory tract infections (OR 1.19; 95% CI 0.98–1.45) or urinary tract infections (OR 0.94; 95% CI 0.57–1.56) was reported with vildagliptin.[19]

Angioedema

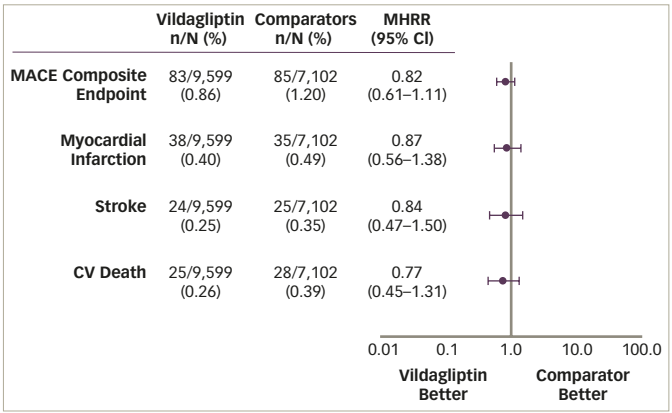
Potential interaction between DPP-4 inhibitors and angiotensin-converting enzyme (ACE) inhibitors has been studied, as both DPP-4 and ACE are actively involved in the metabolism of substance P.[26] To address this, all the angioedema-related AEs in the vildagliptin clinical trial programme were independently and prospectively adjudicated. In the updated vildagliptin pooled safety analysis, the incidence of angioedema was similar between vildagliptin and all comparators (0.3% in both the groups). However, there were more events of angioedema in patients taking vildagliptin concurrently with an ACE inhibitor (0.5%) when compared to comparators (0.3%). The majority of the angioedema cases were mild and resolved with ongoing treatment. Similar findings were also observed with other DPP-4 inhibitors.[27–29]

Acute pancreatitis

Patients with T2DM have a twofold increased risk of acute pancreatitis compared with healthy individuals.[30] Vildagliptin, as all incretin-based therapies, has been extensively evaluated for its pancreatic safety in various pre-clinical and pooled analyses, due to the potential risk of pancreatic events with glucagon like peptide-1 (GLP-1) based therapies, despite the lack of evidence of a causal relationship. Long-term studies in rodents (rats and mice) at approximately 200 times the human exposure dose have shown that vildagliptin is not associated with any evidence of pancreatitis.[31] Similar findings have been observed for all the other GLP-1 based therapies.[32] The pooled safety analysis of data from all phase II–IV studies demonstrated that the incidence of acute pancreatitis was similar for vildagliptin and all comparators (0.3/100 SYEs in both the groups). This was further confirmed by a meta-analysis of 69 trials, wherein there was no increased risk of pancreatitis with vildagliptin relative to comparators (OR 0.97; 95% CI 0.37–2.53; I^2=0%).[19]

Post-marketing cases of pancreatic AEs have been reported with the use of various anti-diabetes agents over time, including GLP-1 based

Figure 1: Incidence and risk ratios for adjudicated composite endpoint of major adverse cardiovascular events and its individual components with vildagliptin (50 mg once daily/twice daily) versus comparators (placebo and active comparators)



CI = confidence interval; CV = cardiovascular; MACE = major adverse CV events consisting of myocardial infarction, stroke and CV death; MHRR = Mantel-Haenszel risk ratio.

therapies.[33] Although an extensive evaluation of non-clinical and clinical data by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) suggested no causal association between pancreatic AEs and GLP-1 based therapies,[34] the risk of acute pancreatitis has been added to the label of all the GLP-1 based therapies. A recent meta-analysis using data from the CV outcomes trials for pooled DPP-4 inhibitors (excluding vildagliptin) demonstrated an increased relative risk of acute pancreatitis (OR 1.79; 95% CI 1.13–2.82)[35] versus placebo, albeit the absolute risk increase was low (0.13%).[35]

Adverse events of special interest for patients with T2DM

Neoplasms

There is evidence indicating an increased risk of cancer in patients with T2DM.[36] Vildagliptin has been evaluated in a range of genotoxicity assays, the results of which did not indicate a genotoxic risk to humans. A 2-year carcinogenicity study in rats, with a dose approximately 200 times the human exposure, did not show an increase in overall tumour incidence.[5] In another study in mice at a dose >240 times the human exposure, a slight increase in the incidence of mammary adenocarcinomas was observed with vildagliptin, the no-effect dose being approximately 500 mg/kg (59-fold human exposure). In the vildagliptin pooled safety analysis, the incidence of all cancers (benign, malignant, and unspecified neoplasms) was similar with vildagliptin and comparators (1.9% in both the groups). There was a numerical imbalance in the incidence of the AE of breast cancer, 0.4 versus 0.2/100 SYEs (vildagliptin versus all comparators); however, the incidence in the all-comparator group was lower than the previously reported incidence of breast cancer from large-scale epidemiological studies,[37,38] which suggests that the imbalance might be a chance finding.

The development of drug-induced carcinogenicity takes a long time, so exposure during RCTs is unlikely to uncover such risks.[39] Using evidence from RCTs and open-label safety studies, the incidence of neoplasms of interest for incretin-based therapies, such as pancreatic cancer, appeared to be lower with vildagliptin than comparators (0.026 versus 0.04/100 SYEs). It is reassuring that more than 10 years of PMS by health authorities and pharmaceutical companies did not suggest an increased risk of cancer with DPP-4 inhibitor therapy.

Cardiovascular safety

DPP-4 inhibitors have been extensively evaluated for their CV safety, and the cumulative evidence has demonstrated CV safety with respect to major adverse CV events (MACE). However, as increased rates of hospitalisation for heart failure (HF) were observed with saxagliptin (saxagliptin, 3.5% versus placebo, 2.8%; hazard ratio [HR] 1.27; 95% CI 1.07–1.51; p=0.007),[40] and alogliptin (3.1% versus placebo, 2.9%; HR 1.07; 95% CI 0.79–1.46),[41] the FDA (5 April 2016) requested for inclusion of the potential increased risk of HF to the labels of saxagliptin and alogliptin.[42] A large, real-world observational study in more than 127,000 patients demonstrated a lower risk for HF-related hospitalisations in DPP-4 inhibitor-treated patients versus sulphonylureas.[43,44]

Analysis of patient-level data pooled from large development programmes, which provide sufficient exposure to the investigational drug and include diverse patient populations and comparators, is a robust way of assessing CV safety.[9] The CV safety of vildagliptin was confirmed in a meta-analysis of independently and prospectively adjudicated CV events from 40 phase III and IV trials enrolling over 17,000 patients. The MHRR for the incidence of MACE with vildagliptin versus comparator was 0.82 (95% CI 0.61–1.11). Similar risk ratios (RRs) were observed for the individual MACE endpoints: myocardial infarction (0.87; 95% CI 0.56–1.38), stroke (0.84; 95% CI 0.47–1.50) and CV death (0.77; 95% CI 0.45–1.131) (see *Figure 1*). The meta-analysis also included patients with advanced disease (T2DM duration more than 10 years), elderly (over 65 years of age), patients with renal impairment and patients with congestive heart failure (CHF).[12] As the events were prospectively adjudicated, and the upper bound of the 95% CI was <1.3, an additional outcome trial was not required to establish the CV safety of vildagliptin.[45]

In the CV meta-analysis, the MHRR for the incidence of confirmed HF events (vildagliptin versus comparator) was 1.08 (95% CI 0.68–1.70), showing no increased risk of HF in vildagliptin-treated patients versus comparators.[12] The safety of vildagliptin in patients with CHF (New York Heart Association [NYHA] class I–III) was also assessed in the 52-week, double-blind, randomised, Vildagliptin In VentrIcular Dysfunction Diabetes (VIVIDD) trial, which showed that vildagliptin was not associated with a change in left ventricular function or worsening of pre-existing CHF.[46] An analytical, non-interventional, multi-database study provided further evidence on the relative safety of vildagliptin in CHF under real-life conditions.[47] The adjusted incidence risk ratios (IRRs) for CHF were close to 1 (0.49–1.03) for vildagliptin versus other non-insulin antidiabetic medications.[47]

Hepatic safety

It is important to establish the hepatic safety of an anti-diabetes agent as patients with T2DM have a high prevalence of liver disease compared to the general population.[48] Evidence from non-clinical toxicology and *in vitro* studies did not indicate a risk of hepatotoxicity with vildagliptin. Since vildagliptin is not metabolised by CYP to a significant extent, the presence of hepatic impairment does not increase the exposure to vildagliptin.[49]

In the pooled safety analysis, the incidence of mild elevations in hepatic enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] ≥3 times upper limit of normal [ULN]) was similar for vildagliptin versus comparators (MHRR 1.19; 95% CI 0.79–1.81), and there was no increased risk for ALT and AST ≥3 ULN, accompanied by bilirubin >ULN (MHRR 0.97; 95% CI 0.16–5.92). The incidence of hepatic AEs (1.6 versus 1.8/100 SYEs, respectively) and SAEs (0.2 versus 0.1/100

SYEs, respectively) was similar between the vildagliptin and comparator groups. In the large, observational EDGE study, liver function test (LFT) abnormalities were infrequent: in the vildagliptin group, 411 of 9,508 patients (4.3%) had bilirubin >ULN versus 190 of 4,691 patients (4.1%) receiving other oral anti-diabetes drugs (OADs).[13] However, a study in patients with T2DM having good glycaemic control (glycated haemoglobin [HbA1c] ≤7.9%) demonstrated that treatment with vildagliptin results in a clinically meaningful decrease in liver triglyceride levels, which was associated with a decrease in plasma ALT and glucose levels.[50] Rare cases of elevations in hepatic enzymes that were generally asymptomatic without clinical sequelae have been observed.[5] Vildagliptin is not recommended in patients with hepatic impairment, including patients with elevated ALT/AST levels.

Renal safety

The renal safety profile of an anti-diabetes agent is yet another important consideration, as chronic kidney disease is a common late-stage complication of progressive T2DM. The increased risk of hypoglycaemia and increased or unpredictable exposure to, not only anti-diabetes, but also other drugs adds to the complexity of managing T2DM in patients with renal impairment. The benefit–risk profile of vildagliptin has been extensively evaluated in patients with renal impairment in studies ranging from PK assessment[51] to clinical safety in patients undergoing haemodialysis.[52] In subjects with moderate or severe renal impairment, the exposure to vildagliptin increases up to twofold, without significantly affecting the maximum concentration (Cmax); accordingly, the effective half-life is increased sufficiently to allow a 50 mg qd dose in patients with moderate to severe renal impairment.[51]

The efficacy and safety of vildagliptin in patients with moderate or severe renal impairment were evaluated in a large (n=525) 1-year randomised trial. The safety profile of vildagliptin 50 mg qd in patients with moderate or severe renal impairment was similar to that of placebo.[25] In another study, vildagliptin and sitagliptin (n=148) showed similar safety profiles in patients with severe renal impairment.[53] There is no evidence that failure to adjust for an increase in exposure with vildagliptin results in renal toxicity.[54] Vildagliptin was well tolerated in patients with severe renal impairment uncontrolled on insulin,[55] in elderly patients (≥75 years) with moderate or severe renal impairment,[56] in patients with new-onset diabetes after transplantation (NODAT)[57] and in patients undergoing haemodialysis,[52] with a similar AE/SAE profile to placebo.

Additional adverse drug reactions from post-marketing experience

Although the assessment of safety using data from controlled studies remains the gold standard, it is important to assess PMS reports in order to continuously evaluate the benefit–risk profile of a drug. Furthermore, as PMS reports contain data from a large number of diverse patients, certain rare AEs that are otherwise not observed during the clinical trial programme, may appear over time. Such events are rare and by virtue of being detected retrospectively, their association with the drug is not conclusively established, as findings are often complicated by co-medications and comorbidities. Some events such as acute pancreatitis and hepatobiliary disorders have been discussed earlier; in addition, other adverse reactions emerging from PMS include skin-related events and musculoskeletal disorders (arthralgia).

Skin-related adverse events

Patients with T2DM have an increased risk of skin-related diseases. Skin lesions in extremities of Cynomolgus monkeys were observed with vildagliptin during early pre-clinical studies at doses of ≥5 mg/kg/day.[4] The lesions were of vascular origin and were not observed in any other animal species.[4] Similarly, the vildagliptin pooled safety analysis did not find an increased incidence of all skin-related AEs with vildagliptin compared to comparators (1.6 versus 1.4/100 SYEs, respectively); however, data from the recently published signal detection studies using pharmacovigilance databases showed increased reports of bullous pemphigoid (BP) in patients using DPP-4 inhibitors.[58,59] The majority of bullous skin lesions were observed in elderly patients,[60] which is consistent with the epidemiology data suggesting increasing age as a risk factor for BP.[61–63] In accordance with the guidance on routine care, monitoring for skin lesions in patients with T2DM treated with a DPP-4 inhibitor is recommended.[5]

Arthralgia

A warning of arthralgia/severe joint pain has been added to the labels of DPP-4 inhibitors[64] on the basis of 33 rare cases of arthralgia/severe joint pain that were observed in a review of the FDA Adverse Event Reporting System database.[65] In the pooled safety analysis, the incidence of arthralgia of any severity was similar for vildagliptin and comparators (3.7% versus 3.3%, respectively). One report suggests a slight increase in the incidence of arthralgia with vildagliptin (OR 1.23; 95% CI 1.02–1.48; I^2=0%; p=0.8).[19]

Conclusions

The efficacy profile, together with a low risk of hypoglycaemia, no weight gain, and absence of increased risk for CV events has established the clinical utility of DPP-4 inhibitors, such as vildagliptin, as anti-diabetes agents for the treatment of patients with T2DM. DPP-4 inhibitors as a class are also the most extensively evaluated oral glucose-lowering agents in terms of their benefit–risk profile which has contributed greatly to evidence-based clinical practice.

The cumulative clinical experience with vildagliptin and DPP-4 inhibitors, in general, has been encouraging in terms of their safety profile. Notably, vildagliptin did not increase the risk of any AEs of interest, such as infections, or those frequently observed in patients with T2DM, such as major adverse CV events. The key known risks include rare cases of mild to moderate elevations in hepatic enzymes, rare cases of angioedema (mostly in patients taking a concomitant ACE inhibitor) that resolved with ongoing treatment and acute pancreatitis, common for the GLP-1 based therapies. The data suggest that these AEs usually resolve upon drug discontinuation. The benefit–risk profile of vildagliptin has not changed considerably over the past 10 years, while the product has been widely used in clinical settings, with only a few reports of rare adverse drug reactions, including pancreatitis, bullous or exfoliative skin lesions and arthralgia, detected by PMS. By virtue of its established safety profile, vildagliptin continues to be a key treatment option for managing diverse patients with T2DM. ❑

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Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study

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Summary

Background Guidelines suggest setting individualised targets for glycaemic control in elderly patients with type 2 diabetes, despite no evidence. We aimed to assess the feasibility of setting and achieving individualised targets over 24 weeks along with conventional HbA_{1c} reduction using vildagliptin versus placebo.

Methods In this multinational, double-blind, 24 week study, we enrolled drug-naive or inadequately controlled (glycosylated haemoglobin A_{1c} [HbA_{1c}] ≥7·0% to ≤10·0%) patients with type 2 diabetes aged 70 years or older from 45 outpatient centres in Europe. Investigators set individualised treatment targets on the basis of age, baseline HbA_{1c}, comorbidities, and frailty status before a validated automated system randomly assigned patients (1:1) to vildagliptin (50 mg once or twice daily as per label) or placebo. Coprimary efficacy endpoints were proportion of patients reaching their investigator-defined HbA_{1c} target and HbA_{1c} reduction from baseline to study end. The study is registered with ClinicalTrials.gov, number NCT01257451, and European Union Drug Regulating Authorities Clinical Trials database, number 2010-022658-18.

Findings Between Dec 22, 2010, and March 14, 2012, we randomly assigned 139 patients each to the vildagliptin and placebo groups. 37 (27%) of 137 patients in the placebo group achieved their individualised targets by education and interactions with the study team alone and 72 (52·6%) of 137 patients achieved their target in the vildagliptin group (adjusted odds ratio 3·16, 96·2% CI 1·81–5·52; p<0·0001). This finding was accompanied by a clinically relevant 0·9% reduction in HbA_{1c} from a baseline of 7·9% with vildagliptin and a between-group difference of –0·6% (98·8% CI –0·81 to –0·33; p<0·0001). The overall safety and tolerability was similar in the vildagliptin and placebo groups, with low incidence of hypoglycaemia and no emergence of new safety signals.

Interpretation This study is the first to introduce and show the feasibility of using individualised HbA_{1c} targets as an endpoint in any type 2 diabetes population. Individualised glycaemic target levels are achievable with vildagliptin without any tolerability issues in the elderly type 2 diabetes population.

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Introduction

Type 2 diabetes mellitus is one of the most common chronic disorders in older adults and the number of elderly individuals with type 2 diabetes is growing worldwide, with a prevalence as high as 18–20% in adults older than 65 years.[1] Definitions of elderly, however, differ vastly and incorporate very different populations with respect to age, frailty status, and comorbidities, therefore each of these factors needs to be taken into account during identification of the most effective therapeutic targets and interventions.[2]

Clinical management of type 2 diabetes in elderly patients presents unique challenges because these patients have a higher burden of diabetes-related morbidity and mortality, microvascular and macrovascular complications, physical disability, cognitive impairment, and frailty.[3,4] Elderly patients with type 2 diabetes are more susceptible to the complications of hypoglycaemia[2,5] and are also frequently subjected to polypharmacy, which in turn increases the risks of drug interactions and adverse reactions.[6] Increasing age is associated with reduced renal function, which further limits therapeutic options in type 2 diabetes.[7] However, untreated or undertreated hyperglycaemia might also present risks of electrolyte abnormalities, dizziness, and falls.[6] In view of these complex treatment decisions, more than half of elderly patients with type 2 diabetes do not achieve conventionally recommended goals of glycaemic control (glycosylated haemoglobin A_{1c} [HbA_{1c}] <7%);[8–11] although, the validity of these targets is now being scrutinised.

In the UK Prospective Diabetes Study, reductions in cumulative microvascular and macrovascular events became apparent only after 9 years,[6,12] whereas in studies that used more aggressive targets,[13–15] macrovascular benefits were not realised at all. Therefore, the most recent set of guidelines emphasise individualisation of HbA_{1c} targets based on patients' characteristics and suggest less rigorous individualised care rather than tight glycaemic targets in

elderly patients with limited life expectancy.[6,7,16] However, these guidelines largely use data extrapolated from patients younger than 70 years with type 2 diabetes because most randomised clinical trials exclude frail elderly patients with poor health status, leading to gaps in understanding about the most appropriate treatment regimens and the effects of glycaemic control in this population.[6,16] Furthermore, no trials using individualised targets or assessments of tolerability of any individualised treatments have been reported.

We aimed to assess the feasibility of setting and achieving investigator-defined individualised treatment targets for a period of 24 weeks in elderly patients with type 2 diabetes (drug-naive or inadequately controlled on oral agents), with the addition of a single oral agent. The drug of choice was the selective dipeptidyl peptidase 4 (DPP4) inhibitor vildagliptin because it has well documented efficacy and safety in elderly patients with type 2 diabetes.[17]

Methods

Study design and patients

In this 24 week, multicentre, randomised, double-blind, placebo-controlled study, patients were recruited from 45 outpatient centres in seven European countries (Belgium, Bulgaria, Germany, Finland, Slovakia, Spain, and UK). Patients aged 70 years or older with type 2 diabetes who were drug-naive or inadequately controlled, with HbA_{1c} levels of 7·0% or greater and 10·0% or less, fasting plasma glucose (FPG) of less than 15 mmol/L (270 mg/dL), and body-mass index of 19–45 kg/m^2 at screening (visit 1) were eligible. Patients who had taken no oral antidiabetic drugs (OADs) for at least 12 weeks before screening and no OADs for more than 3 consecutive months at any time in the past were regarded as drug-naive. Patients taking OADs at the time of screening were required to have had stable doses for at least 12 weeks before screening. The exclusion criteria included use of insulin treatment (>7 consecutive days) or incretin-based therapies in the preceding 12 weeks, use of corticosteroids within 8 weeks, or use of growth hormone within 6 months of the screening visit. Patients with acute metabolic diabetic disorders, myocardial infarction, coronary artery bypass surgery, or stroke within 6 months; unstable angina within 3 months; congestive heart failure (New York Heart Association classification of III or IV); malignancy within 5 years; or liver disease such as cirrhosis or hepatitis were excluded from the study. Substantial laboratory abnormalities including liver function tests, renal dysfunction as suggested by reduced glomerular filtration rate (<30 mL/min per 1·73 m^2), or positive hepatitis B or C tests also precluded participation.

This trial was done in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles laid down in the Declaration of Helsinki. An independent ethics committee or institutional review board at each research site reviewed the study protocol. Eligible patients were included in the study only after they had provided written informed consent.

Randomisation and masking

After a screening period of up to 2 weeks, eligible patients were randomly assigned to a treatment group (week 0) and followed up at four in-person visits (weeks 4, 12, 18, and 24) with an interim telephone contact at week 8. The randomisation list was produced by an interactive response technology provider (Cenduit, Durham, NC, USA) using a validated automated system that randomly assigned patients in a 1:1 ratio to receive either vildagliptin or placebo. The randomisation was stratified on the basis of the patient's background OAD treatment into drug-naive (no background OAD), sulphonylurea monotherapy, or all other background OADs (inclusive of sulphonylurea in a combination therapy). Patients, investigators, people doing the assessments, and data analysts were masked to the treatments from randomisation to database lock. The identity of the treatments was concealed by the use of study drugs that were identical in schedule of administration, packaging, labelling, appearance, taste, and odour.

Procedures

Patients in the drug-naive and other background OAD groups received vildagliptin (50 mg) twice daily or placebo, whereas patients in the sulphonylurea monotherapy group received vildagliptin (50 mg) once daily or placebo. Study drug dose adjustments or interruptions were not permitted. Patients remained on stable doses of OADs for the duration of the study. Study drug was discontinued and the patient withdrawn from the study if the investigator decided that continuation would result in a substantial safety risk for that patient. Insulin or any OAD (excluding incretin analogues and DPP4 inhibitors) could be used as rescue medication by the investigator at any time after randomisation if patients did not achieve a satisfactory therapeutic effect. However, efficacy data for patients receiving rescue medication were censored from the day after the rescue medication was started.

The two coprimary efficacy variables in this study were proportion of patients reaching their investigator-defined individualised HbA_{1c} target and the conventional HbA_{1c} reduction from baseline to week 24. Secondary efficacy parameters included change in FPG from baseline to study endpoint. We also explored investigator-defined treatment targets based on patient subgroups such as age, baseline HbA_{1c}, and frailty status. HbA_{1c}, FPG, bodyweight, vital signs, and liver function tests were measured at each study visit. Standard haematology and biochemistry laboratory assessments were done at screening and at weeks 0, 12, and 24, and urinalysis was done at weeks 0, 12, and 24.

All adverse events (AEs) and their severity, serious AEs (SAEs), and their presumed relation with the study drug were monitored and recorded at each study visit.

Particular attention was paid to safety areas thought to be of potential concern for DPP4 inhibitors[18] and elderly patients,[17] such as AEs associated with the liver, infections, pancreatitis, muscle, neuropsychiatric problems, lactic acidosis, skin or vascular problems, and cardiovascular or cerebrovascular events. We defined hypoglycaemia as symptoms suggestive of hypoglycaemia and a self-monitored plasma glucose measurement of less than 3·1 mmol/L. We defined severe hypoglycaemia as an episode that needed the assistance of another person or admission to hospital with or without a plasma glucose measurement of less than 3·1 mmol/L.

At baseline (visit 2), an individualised 24 week HbA_{1c} target was defined by the investigators for each of their patients, taking into account age of the patient, frailty status, comorbidities, and baseline HbA_{1c} values; most guidelines recommend using these factors to personalise treatments. Importantly, these investigator-defined individualised HbA_{1c} targets were based on the physicians' clinical judgment and local recommendations for glycaemic targets. Since this was not a treat-to-target protocol, the background medications of the patients were not titrated in an attempt to reach the individualised target. Frailty status of the patients was assessed with a modified version of a frailty phenotype proposed by Fried and colleagues.[19] Patients were regarded as frail if they had any two of the following three variables: unintentional weight loss (>4·5 kg or >5% loss of bodyweight in the past year), slow walking speed, and poor grip strength as measured by a dynamometer. All randomly assigned patients were educated about the management of their diabetes, the meaning of their individualised treatment targets, symptoms of hyperglycaemia and hypoglycaemia, possible triggers of hypoglycaemia, and appropriate treatment for events.

HbA_{1c} (measured by ion exchange high-performance liquid chromatography) and FPG samples were sent for analysis to a central laboratory (Covance, Geneva, Switzerland). Patients measured their blood glucose with one of several recommended calibrated home glucose monitors when they had hypoglycaemic symptoms and at other timepoints recommended by the investigator. Patients recorded the event in a glycaemic study diary, including the glucose value and any relevant associated information.

Statistical analysis

We expected a small sample size at most individual study centres, so all centres within the same country were combined to form a pooled centre. We analysed the proportion of patients achieving their individualised HbA_{1c} target at week 24 in each treatment group with a logistic regression model including terms for treatment, baseline HbA_{1c}, background OAD, and country. We then calculated the odds ratio (OR), defined as the odds of responding in one group divided by the odds of responding in the second group. We compared the change in HbA_{1c} from baseline to week 24 between patients assigned to vildagliptin and those assigned to placebo with an ANCOVA model that included terms for treatment, baseline HbA_{1c}, background OAD, and countries. We assessed the coprimary efficacy variables simultaneously for superiority compared with placebo with two-sided tests and a 5% significance level shared between the two variables, with 3·8% significance for the individualised treatment target and 1·2% for the difference in HbA_{1c}. The primary objective was fulfilled if either of the coprimary endpoints was met. We also analysed the risk ratio for the number of patients who reached the investigator defined HbA_{1c} target at study endpoint using a log linear regression model including terms for treatment, baseline HbA_{1c}, background OAD strata, and countries. We analysed the primary efficacy variables using data from the intention-to-treat population, which included all randomly assigned patients who received at least one dose of study drug and had at least one postbaseline efficacy measurement. We also did analyses based on the per-protocol set to assess the robustness of the conclusions.

We aimed to randomly assign about 280 patients (140 patients per group) to achieve a sample size of 238 completed patients (119 per group), assuming a drop-out rate of 15%. This sample size ensured 80% power at a 3·8% significance level for the ability to achieve the individualised treatment target, assuming about a

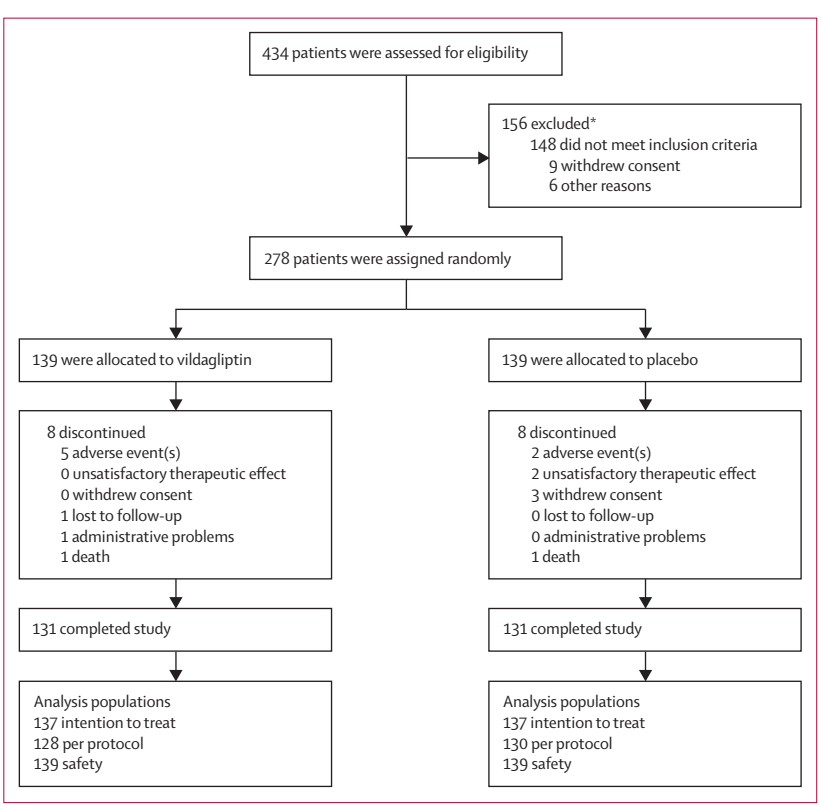

Figure 1: **Trial profile**
*Some patients were excluded for more than one reason.

	Vildagliptin (n=139)	Placebo (n=139)
Age (years)	75·1 (4·3)	74·4 (4·0)
Range	70·0–97·0	70·0–89·0
Men	73 (52·5%)	53 (38·1%)
Race		
White	135 (97·1%)	134 (96·4%)
Other	4 (2·9%)	5 (3·6%)
Systolic blood pressure (mm Hg)	137·0 (13·3)	137·5 (15·8)
Diastolic blood pressure (mm Hg)	76·8 (8·3)	76·9 (7·9)
Body-mass index (kg/m²)	29·1 (3·8)	30·5 (4·8)
HbA_{1c} (%)	7·9 (0·8)	7·9 (0·7)
Fasting plasma glucose (mmol/L)	9·6 (2·3)	9·9 (2·1)
Duration of type 2 diabetes (years)	12·2 (7·9)	10·6 (6·9)
Range	1·3–35·0	0·3–32·8
GFR (MDRD) (mL/min/1·73 m²)		
Normal (>80)	34 (24·5%)	31 (22·3%)
Mild (≥50 to ≤80)	86 (61·9%)	87 (62·6%)
Moderate (≥30 to <50)	19 (13·7%)	21 (15·1%)
Frailty status		
Yes	12 (8·6%)	14 (10·1%)
No	126 (90·6%)	123 (88·5%)
Missing	1 (0·7%)	2 (1·4%)

Data are mean (SD) or number (%). HbA_{1c}=glycosylated haemoglobin A_{1c}. GFR (MDRD)=glomerular filtration rate estimated using the modification of diet in renal disease formula.

Table 1: **Baseline demographics and clinical characteristics**

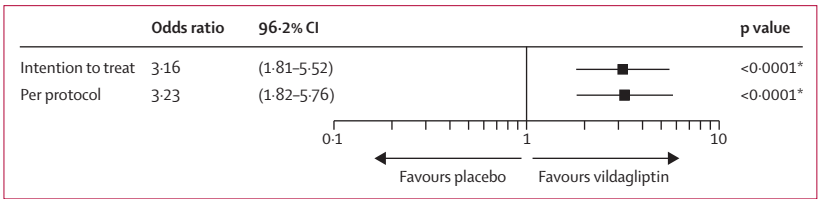

Figure 2: **Odds ratio for proportion of patients achieving individualised HbA_{1c} targets after 24 weeks**
Odds ratios, associated CI, and p values were calculated from a logistic regression model containing terms for treatment, baseline HbA_{1c} (centred by subtracting the overall mean baseline HbA_{1c} of all treatment groups), background oral antidiabetic drug strata, and pooled centres to compare the treatment effect. Squares show odds ratios for intention-to-treat analysis and per-protocol analysis; the lines show the 96·2% CI. Equivalent risk ratios for the number of patients who reached the investigator-defined HbA_{1c} target at study endpoint were 1·92 (96·2% CI 1·29–2·86; p=0·0013) in the intention-to-treat analysis and 1·91 (1·27–2·86; p=0·0017) in the per-protocol analysis. *Indicates statistical significance at two-sided 3·8% level.

19–22% percentage point difference in response rate between the vildagliptin and placebo groups. This sample size also ensured 90% power with a significance level of 1·2% to detect a between-group difference of half a standard deviation in HbA_{1c}. A difference of less than this amount, although of scientific interest, would not be clinically relevant. The endpoint for both primary efficacy variables was defined as the final available post-randomisation assessment obtained at any visit before or at the start of rescue medication use up to the visit at week 24.

We analysed the secondary efficacy variables with the same ANCOVA model as specified for the primary efficacy variable. Differences between vildagliptin and placebo were based on a two-sided 5% significance level. We used the last observation carried forward method to handle missing data due to early discontinuation or data censoring.

We produced a descriptive summary of the proportion of patients meeting individualised HbA_{1c} targets by treatment and baseline characteristic subgroups (age, baseline HbA_{1c}, frailty status). We also used a single multivariate model to analyse the effect of baseline characteristics on HbA_{1c} target setting on the intention-to-treat population. The model was based on the variables, which investigators were trained to follow, that should have affected target setting (target setting = frailty status [yes or no] + age [<75 or ≥75 years] + sex + duration of diabetes + screening HbA_{1c}).

We summarised safety data by treatment group for the safety set (including all patients who received at least one dose of study drug). Hypoglycaemia events were included in all AE summaries. We did all calculations with Proc Power procedure in SAS version 9.2.

The study is registered with ClinicalTrials.gov, number NCT01257451, and the European Union Drug Regulating Authorities Clinical Trials database, number 2010-022658-18.

Role of funding source

The sponsor of the study participated in the study design, data collection, data review, data analysis, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 22, 2010, and March 14, 2012, 434 individuals were screened and 278 participants were included in the study: 139 patients in each of the vildagliptin and placebo groups (figure 1). Most of the 156 patients excluded from the study either had unacceptable laboratory values (117 [75%]) or did not meet diagnostic or severity criteria (23 [15%]). Only eight (5·8%) patients in each group discontinued the study prematurely. The vildagliptin and placebo groups were similar for all patient demographic and background characteristics at baseline (table 1). The study cohort was representative of the overall elderly type 2 diabetes population[16] with a mean age of 74·8 years (SD 4·17; range 70·0–97·0), mean duration of diabetes of 11·4 years (SD 7·47; range 0·3–35·0), 213 (76·6%) patients with mild or moderate renal impairment, and 26 (9·4%) frail patients. Relevant medical history and comorbid disorders were similar in the two treatment groups with respect to hypertension (117 [84·2%] patients in the vildagliptin group *vs* 115 [82·7%] in the placebo group), dyslipidaemia (37 [26·6%] *vs* 29 [20·9%]), hypercholesterolaemia (22 [15·8%] *vs* 22 [15·8%]), hyperlipidaemia (36 [25·9%] *vs* 28 [20·1%]), myocardial ischaemia (22 [15·8%] *vs* 24 [17·3%]), peripheral neuropathy

(30 [21·6%] *vs* 36 [25·9%]), and osteoarthritis (27 [19·4%] *vs* 28 [20·1%]). As expected, almost all patients were using concomitant medications, with a substantial majority taking antihypertensive and lipid-lowering medications. Metformin and sulphonylureas were the most frequently used OADs; of the randomly assigned patients, nearly half were taking metformin, whereas a third were using sulphonylureas.

In this elderly cohort, the mean individualised HbA_{1c} targets set by the investigators were around 7·0% for both treatment groups, 0·9% (range –4·4 to –0·1) lower than the mean baseline HbA_{1c} of 7·9% in each treatment group. In the placebo group, 37 (27%) of 137 patients achieved their individualised targets as a result of education and interactions with the study team alone; this number was almost double, at 72 (52·6%) of 137, in the vildagliptin group. The adjusted OR of achieving the individualised target was 3·16 (96·2% CI 1·81–5·52; p<0·0001; figure 2). The number of patients reaching their individualised targets was higher in the vildagliptin group than in the placebo group, independent of their baseline characteristics (table 2). The risk ratios for the number of patients who reached the investigator-defined HbA_{1c} target at study endpoint were 1·92 (96·2% CI 1·29–2·86; p=0·0013) in the intention-to-treat analysis and 1·91 (1·27–2·86; p=0·0017) in the per-protocol analysis.

In terms of the conventional HbA_{1c} reduction from baseline to study endpoint, patients in the placebo group achieved a sizable change of –0·3% from a baseline of 7·9%. Vildagliptin consistently maintained HbA_{1c} at a lower level than did placebo (appendix) and resulted in a change of –0·9% from a baseline of 7·9%, with a statistically significant difference compared with placebo of –0·6% (98·8% CI –0·81 to –0·33; p<0·0001; figure 3). The study thus met both its coprimary endpoints. Analyses in the per-protocol study population showed very similar results for both primary endpoints. Both the vildagliptin and the placebo group showed a mean decrease in FPG at study endpoint; the difference between treatment groups of –0·9 mmol/L was statistically significant (p<0·0001; appendix). In terms of the effect of baseline characteristics on HbA_{1c} target setting, the only variables with a significant effect were sex (p=0·0258), with men set more aggressive targets than women, and HbA_{1c} (p<0·0001; appendix).

Overall safety and tolerability in the vildagliptin and placebo groups were generally similar in this elderly cohort (table 3). The number of patients with one or more AEs in the vildagliptin group (66 [47·5%]) was similar to that in the placebo group (63 [45·3%]). The number of patients reporting dizziness was numerically greater in the vildagliptin group than in the placebo group. Most AEs were assessed as mild or moderate and not related to the study drug. SAEs were reported for a low number of patients in both treatment groups. We noted no trends in the occurrence of SAEs, which were scattered across many system organ classes (appendix). AEs leading to discontinuation were few and similar in both treatment groups. Two patients died during the study, one in each study group, as a result of sudden cardiac death (in the vildagliptin group) and multiorgan failure (placebo). Neither case of death was suspected by the investigator to be related to the study drug. An analysis of specific safety topics of interest revealed no differences between the vildagliptin and placebo groups except that the proportion of patients reporting infections or infestations was a third higher in the placebo group (24 [17·3%]) than in the vildagliptin group (18 [12·9%]). We noted no reported cases of pancreatitis or clinically significant hepatic-related events.

The incidence of hypoglycaemic events was low overall: three (2·2%) of 139 patients in the vildagliptin group and one (0·7%) of 139 patient in the placebo group. All hypoglycaemic events occurred in patients using concomitant sulphonylureas. No severe hypoglycaemic events were reported in either group.

	Vildagliptin (n=137)	Placebo (n=137)
Age (years)		
<75	33/67 (49·3%)	22/86 (25·6%)
≥75	39/70 (55·7%)	15/51 (29·4%)
HbA_{1c} levels		
≤8%	46/83 (55·4%)	27/86 (31·4%)
>8%	26/54 (48·1%)	10/51 (19·6%)
≤9%	65/125 (52·0%)	34/128 (26·6%)
>9%	7/12 (58·3%)	3/9 (33·3%)
Frailty status		
Frail	5/12 (41·7%)	6/14 (42·9%)
Non-frail	67/124 (54·0%)	30/121 (24·8%)

Data are number (%). HbA_{1c}=glycosylated haemoglobin A_{1c}.

Table 2: **Proportion of patients achieving individualised HbA_{1c} targets, according to baseline characteristics**

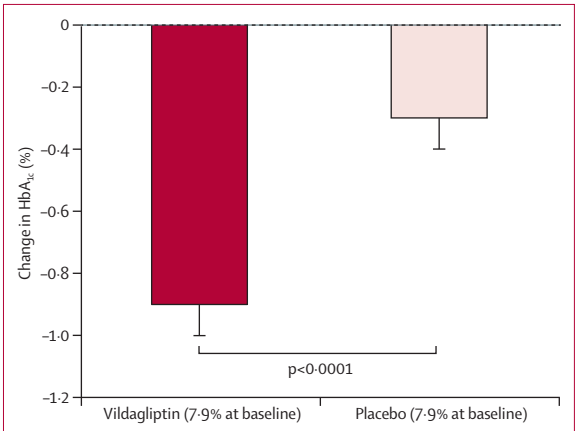

Figure 3: **Change in HbA_{1c} values from baseline to week 24 in the intention-to-treat population**
Bars show least squares mean; the lines from the bars show SE.

See Online for appendix

	Vildagliptin (n=139)	Placebo (n=139)
Overall*	66 (47·5%)	63 (45·3%)
SAEs†	8 (5·8%)	5 (3·6%)
Discontinuations due to AEs	6 (4·3%)	3 (2·2%)
Deaths	1 (0·7%)	1 (0·7%)
AEs (of any severity) in ≥5% of participants in any treatment group		
Dizziness	11 (7·9%)	3 (2·2%)
Headache	8 (5·8%)	4 (2·9%)
Nasopharyngitis	7 (5·0%)	7 (5·0%)
Any predefined risk‡	21 (15·1%)	24 (17·3%)
Hepatic-related AEs	0	0
Infection-related AEs	18 (12·9%)	24 (17·3%)
Pancreatitis-related AEs	0	0
Muscle-related AEs	1 (0·7%)	0
Neuropsychiatric-related AEs	1 (0·7%)	0
Lactic-acidosis-related AEs	0	0
Skin or vascular-related AEs	1 (0·7%)	0
Cardiovascular or cerebrovascular AEs	5 (3·6%)	3 (2·2%)

Data are number (%). AE=adverse event. *A patient with several occurrences of an AE on one treatment is counted only once in the AE category. †A detailed listing of the SAEs is available in the appendix. ‡Acute pancreatitis-related AEs, hepatic-related AEs, infection-related AEs, lactic-acidosis-related AEs, muscle-related AEs, neuropsychiatric-related AEs, and skin or vascular-related AEs were defined as events of predefined risk.

Table 3: **Treatment-emergent AEs in the safety analysis population**

No notable changes or abnormalities of any of the assessed vital-sign variables were recorded, and mean bodyweight hardly changed throughout the study in both treatment groups (79·9 kg at baseline and 79·8 kg at study endpoint in the vildagliptin group *vs* 80·7 kg at baseline and 79·7 kg at study endpoint in the placebo group; n=138 in each group).

Discussion

This study shows the feasibility of individualised treatment targets in clinical practice. Treatment guidelines for type 2 diabetes started proposing individualised care only after the results from landmark clinical trials[13–15,20] came into focus (panel). However, gaps exist in the knowledge with respect to absence of any large-scale intervention studies in older adults, patients with several comorbidities and geriatric syndromes, classification of older adults with increasing risk of mortality, and patients in dependent living situations.[6,16] These unique treatment challenges have not been particularly well addressed in clinical studies. Therefore, an understanding of the importance of assessing individualised target setting is needed, especially in a more fragile elderly population, as is comparing individualised target setting with conventional methods of assessing antihyperglycaemic therapies.

Our study introduced the unique endpoint of investigator-defined individualised HbA_{1c} targets in a pragmatic clinical trial setting, which parallels the guidelines for treatment of elderly patients with type 2 diabetes. The study population seemed to have well controlled type 2 diabetes with a mean baseline HbA_{1c} of 7·9%, and the mean investigator-defined individualised targets were about 0·9% lower than the mean baseline HbA_{1c}. This mean target of around 7·0% was substantially lower than we expected for this elderly population. All investigators were trained in the setting of individualised targets on the basis of clinical judgment, while including age, frailty status, comorbidities, baseline HbA_{1c}, and local treatment guidelines in their decision-making process. Despite this requirement to set a balanced target, the adherence to the mean 7·0% target suggests that investigators were greatly influenced by the conventional guideline-stipulated stringent HbA_{1c} target. This finding shows that synchronisation of the local and national guidelines with the global treatment guidelines[6,7,16] recommending less aggressive glycaemic targets for elderly patients with type 2 diabetes is needed, and calls into question the practical application of these global guidelines.[7,16] We believe, however, that part of the issue might lie in the novelty of this study; despite guidelines, recommendations, and the study-specific training provided, no evidence for less aggressive targets is available.

After 24 weeks of treatment, a quarter of the patients achieved their individualised targets by simple education and interactions with a study team focusing on personalised care rather than target number chasing. After adjustment for baseline characteristics, addition of vildagliptin increased the ability to achieve the individualised targets by more than three times without major tolerability issues. The vildagliptin group consistently had a higher proportion of patients who had reached their individualised targets than did the placebo group, irrespective of age, baseline HbA_{1c}, and frailty status. During the course of this study, patients given vildagliptin also achieved clinically relevant reductions in HbA_{1c} (–0·9%) and FPG. Our findings support previously reported efficacy of vildagliptin in elderly patients with type 2 diabetes.[17,21,22] We should emphasise that physicians set rather aggressive targets even in these relatively well controlled elderly patients. Thus a substantial proportion of patients achieving their individualised HbA_{1c} targets were also very close to the conventional target.[7]

As expected, most patients in our study had a long duration of diabetes, had several diabetes-related or other comorbidities, and needed polypharmacy at baseline. Most of the patients also had mild or moderate renal impairment. Despite these challenging factors, the safety and tolerability of vildagliptin in this cohort was similar to that of placebo. Most of the reported AEs and SAEs were isolated events, generally expected in an elderly type 2 diabetes population, and did not show any particular clinically relevant trends. Although the

vildagliptin group had numerically more AEs suspected to be drug-related or that led to discontinuation than did the placebo group, most AEs were mild to moderate, occurred at a far lower frequency than expected, and seemed to be less frequent than reported in other studies with DPP4 inhibitors,[23] although such a comparison does have its limitations. Our study further corroborates the safe profile of vildagliptin reported in two separate pooled analyses of vildagliptin studies in elderly patients with type 2 diabetes.[17,21]

Hypoglycaemia and its related effects are of special concern in elderly patients with type 2 diabetes. This population of patients has fewer adrenergic symptoms such as sweating and tremor than do younger patients with diabetes, and more neuroglycopenic symptoms such as confusion, which make hypoglycaemia more difficult to recognise.[2,6] Hypoglycaemic episodes tend to be more severe in elderly patients, possibly due to impaired counter-regulatory response, which can lead to serious events such as falls and fractures and potentially increase cardiovascular risk.[3] In our study, despite the stringent and clinically significant glycaemic control, the overall incidence of hypoglycaemic events was low and similar in both treatment groups and no severe hypoglycaemic events were reported. All patients who had hypoglycaemic episodes were taking high doses of sulphonylureas. Our study supports the very low incidence of hypoglycaemia reported previously with vildagliptin in the elderly population[17,21,22] or in other highly susceptible patient populations such as patients with moderate or severe renal impairment.[24]

In our study we used broad inclusion criteria consistent with existing labelling for vildagliptin to reflect a real-world setting, which ensured that we had study patients that seemed mostly representative of the overall elderly type 2 diabetes population who were likely to be prescribed vildagliptin irrespective of their participation in this study. However, the small sample size and short study duration were potential limitations of this study. We also did not measure compliance with polypharmacy, which could potentially affect such an elderly population. A further limitation of this study was that the frailty status of participants was based on just one assessment. Although the proportion of frail individuals in the study cohort was similar to that in the general population,[19] it seemed to limit our analyses of HbA_{1c} targets and change in frailty status in this subgroup (data not shown). It will, therefore, be interesting to study an elderly type 2 diabetes population with a higher proportion of frail patients in a clinical trial setting. More studies of this kind are needed to better understand individualised glycaemic targets and to lay the foundation for stronger treatment guidelines in elderly patients with type 2 diabetes.

In conclusion, our study reports the use of individualised targets in a clinical trial setting. Patients treated with vildagliptin were twice as likely to achieve their individualised treatment target (adjusted OR 3·16), accompanied by clinically relevant reductions in HbA_{1c}.

Panel: Research in context

Systematic review

We searched PubMed with English search terms including "elderly", "Type 2 Diabetes", "individualized", "treatment targets", and "treatment guidelines" for articles published between April, 2003, and April, 2013. We identified three guidelines suggesting individualisation of targets for glycaemic control in elderly patients with type 2 diabetes with limited life expectancy.[6,7,16] We found no evidence to support such an approach, which was emphasised in two of the guidelines.[6,16] Furthermore, we found no reports assessing the feasibility of individualised target setting in a clinical trial context.

Interpretation

This trial is a pragmatic study, in which we assessed the feasibility of setting and achieving investigator-defined individualised treatment targets for a period of 24 weeks in elderly patients with type 2 diabetes. Once set, a single oral agent, vildagliptin, was used to achieve the targets. Our results support the guidelines' recommendations[6,7,16] and show that individualised glycaemic target levels are achievable with vildagliptin without any tolerability issues in the growing elderly type 2 diabetes population.

Contributors

WDS represented the study investigators and participated in the study design, data collection, data review, initial data interpretation, and overall clinical interpretation. PMP played a crucial part in the study design, overall planning and implementation of the trial, data collection, initial data interpretation, and drafting of the manuscript. VL and WK contributed to study design and initial data interpretation. M-JH contributed to initial data interpretation. All authors were involved in manuscript revisions and are responsible for intellectual content.

Conflicts of interest

WDS has received research grants from Novartis and Novo-Nordisk, and speaker honoraria from Novartis, Novo-Nordisk, and Boehringer Ingelheim. WK, VL, M-JH, and PMP are employed by and own shares in Novartis.

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original article

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ORIGINAL ARTICLE

Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial

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Aim: Assess safety/tolerability and efficacy of the DPP-4 inhibitor vildagliptin in 515 patients with type 2 diabetes mellitus (T2DM) and moderate or severe renal impairment (RI).
Methods: Double-blind, randomized, parallel-group, placebo-controlled, 24-week clinical trial assessing safety and efficacy of vildagliptin (50 mg qd) added to current antidiabetic therapy, in patients with T2DM and moderate or severe RI (GFR $\geq$ 30 to <50 or <30 ml/min/1.73 m^2).
Results: The study population comprised of 165 and 129 patients with moderate RI and 124 and 97 patients with severe RI randomized to vildagliptin and placebo, respectively, with most patients receiving background insulin therapy (68 and 81% for moderate and severe RI, respectively). After 24 weeks, the between-treatment difference in the adjusted mean change in A1C was -0.5 ± 0.1% ($p < 0.0001$) in moderate RI (baseline A1C = 7.9%) and -0.6 ± 0.1% ($p < 0.0001$) in severe RI (baseline A1C = 7.7%). In patients with moderate RI, similar proportions of those receiving vildagliptin or placebo experienced any AE (68 vs. 73%), any SAE (9 vs. 9%), any AE leading to discontinuation (3 vs. 5%) or death (1 vs. 1%). This was also true for patients with severe RI: AEs (73 vs. 74%), SAEs (19 vs. 21%), AEs leading to discontinuation (9 vs. 6%) and death (2 vs. 4%).
Conclusions: In this 24-week study of 515 patients with T2DM and moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo. Further, relative to placebo, vildagliptin elicited a statistically and clinically significant decrease in A1C in patients with moderate or severe RI.
Keywords: adverse drug reactions, antidiabetic drug, diabetic nephropathy, DPP-IV inhibitor, GLP-1, type 2 diabetes

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Introduction

Kidney disease is a very common co-morbidity of type 2 diabetes mellitus (T2DM) [1] and renal impairment (RI) limits the therapeutic options for patients with T2DM [2]. Metformin is contraindicated in patients with moderate to severe RI, as are some sulfonylureas (SUs) [3]. Thiazolidinediones (TZDs) should be used with caution due to their propensity to cause fluid retention. α-Glucosidase inhibitors (AGIs) are not recommended for use in patients with RI because of increased exposure and lack of safety data. Even insulin therapy is more difficult to use in renally impaired patients because insulin is cleared to a major extent by the kidneys.

Because of the high prevalence of kidney disease in diabetes, and the limited therapeutic options, it is important to establish the safety and efficacy of any new antidiabetic agent in patients with RI. The newest class of oral antidiabetic agents (OADs) is the DPP-4 inhibitors. While the efficacy and safety of DPP-4 inhibitors has been studied extensively and shown convincingly in patients with T2DM and normal renal function [4–8], information about DPP-4 inhibitors in patients with moderate to severe renal impairment is limited to two relatively small studies [9,10]. In contrast, the current much larger study aimed to establish the safety/tolerability and efficacy of the DPP-4 inhibitor vildagliptin in 515 patients with T2DM and moderate or severe RI.

The main route of elimination of vildagliptin is metabolism, with only approximately 25% of the drug excreted by kidneys [11]. Thus, it is not surprising that exposure to vildagliptin increases only ~2-fold in patients with severe RI relative to healthy volunteers with little change in C_{max} (unpublished). As maximal efficacy [12,13] and established safety [5–7,14] are seen with vildagliptin given at a dose of 50 mg twice daily in patients with normal renal function, a dose of 50 mg once daily was chosen for the present study to assess the tolerability,

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safety and efficacy of vildagliptin added to current therapy in patients with T2DM and moderate or severe RI.

Methods

Patients and Study Design

This was a multi-centre, randomized, double-blind, parallel group, placebo-controlled clinical trial of vildagliptin (50 mg qd) in patients with T2DM and moderate or severe RI (estimated Glomerular Filtration Rate [eGFR] by the Modification of Diet in Renal Disease [MDRD] formula $\geq$30 to $<$50 ml/min/1.73 m^2 and $<$30 ml/min/1.73 m^2, respectively). Adult patients (age 18–85 years) with T2DM, either untreated (no therapy in previous 8 weeks) or treated with an SU, AGI, TZD, insulin, meglitinide or a combination of agents were eligible, provided that their dosages were stable for the previous 4 weeks, A1C was between 6.5 and 10% and BMI was between 18 and 42 kg/m^2. Patients were excluded if their fasting plasma glucose (FPG) was $\geq$15 mmol/l, they had a history of renal transplant, significant cardiovascular history within 6 months, active liver disease or abnormal liver tests (ALT, AST or bilirubin 2$\times$ upper limit of normal [ULN]). The initial protocol excluded patients undergoing any dialysis, but this was subsequently amended to remove that restriction.

After a 2-week single-blind, placebo run-in period, eligible patients were randomized to vildagliptin (50 mg) or placebo once daily (final allocation of 1.3 : 1). Rescue medication (insulin addition or intensification) was administered after Week 4 if FPG 15 mmol/l, at Week 8 if FPG 13.3 mmol/l and at Week 16, if FPG 12.2 mmol/l.

Safety Assessments

Assessment of safety and tolerability of vildagliptin (50 mg qd) in patients with T2DM and moderate or severe RI was the primary objective of this study. All treatment-emergent AEs were recorded and assessed by the investigator as to severity and potential relationship to study drug. Particular attention was paid to safety areas considered to be of potential concern for DPP-4 inhibitors (i.e. hepatic, infections, skin, pancreatitis [7]) as well as edema and CV safety, which were considered of interest in this renally impaired population and which were previously analysed in patients with normal renal function or mild RI [5,6]. 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 assistance of another party (whether or not a confirmatory SMBG measure was available).

Efficacy Assessments

Efficacy variables, A1C and FPG, were assessed at every visit. An analysis of responder rates was also performed to assess the percentage of patients achieving A1C $<$7.0%.

Statistical Analysis

The adjusted mean changes (AMΔ) in A1C and FPG from baseline to rescue-censored endpoint (with last observation carried forward for data censored at initiation of rescue medication) were compared between treatments for patients stratified by severity of RI, using an ANCOVA model with baseline value as covariate and background therapy, pooled centre and treatment as factors. The safety data were summarized descriptively by treatment and RI severity. The incidences of events included in the safety topics of interest for DPP-4 inhibitors were compared between treatments, stratified by severity of RI, using Fishers exact test. Safety analysis was performed on all collected data regardless of rescue medication use.

Ethics and Good Clinical Practice

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practice guidelines. The study protocol was approved by an independent ethics committee/IRB at each site and all patients provided written informed consent.

Results

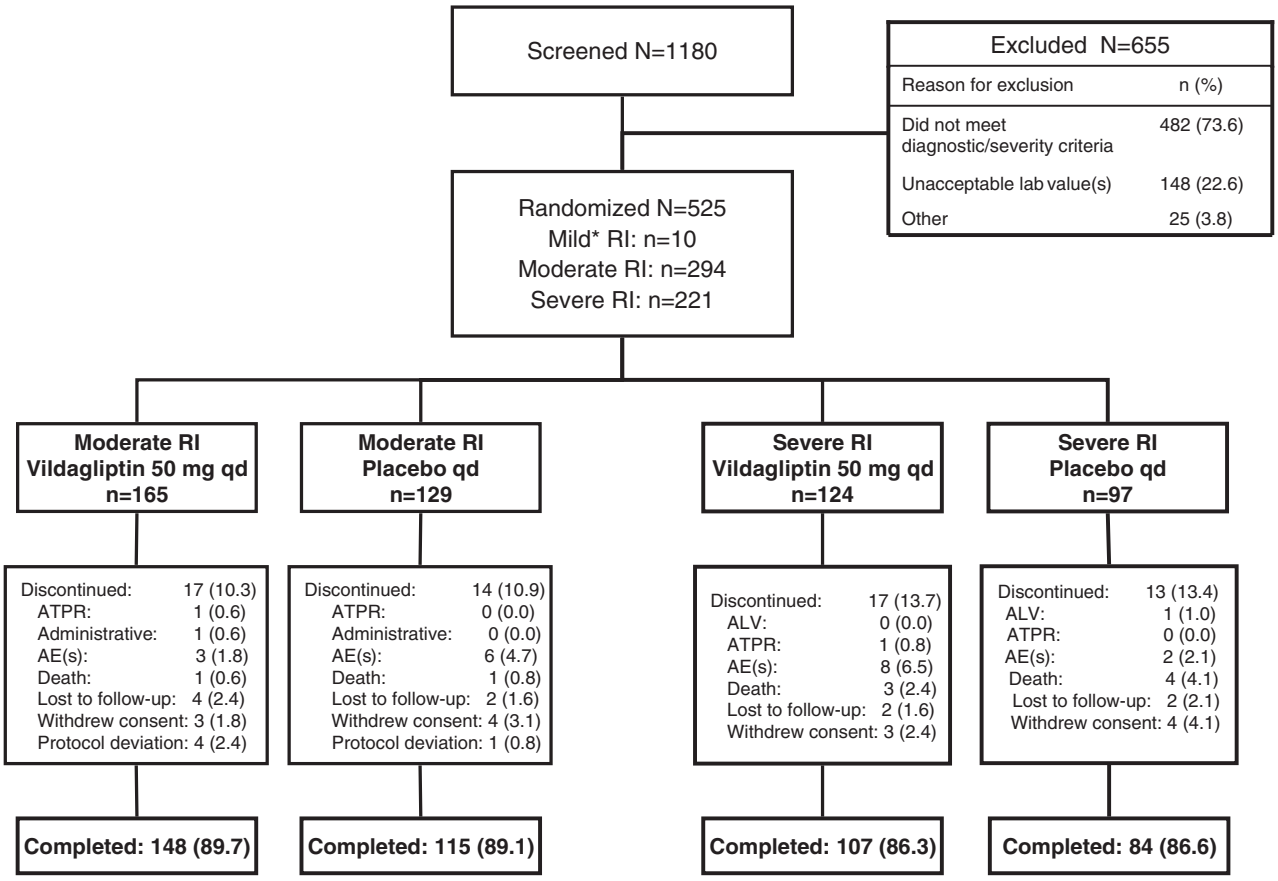
Patient Disposition, Demographic and Baseline Characteristics

Patient disposition from screening through study completion is illustrated in the flow chart shown in figure 1. A total of 525 patients were randomized: 165 patients with moderate and 124 patients with severe RI to vildagliptin 50 mg qd, 129 patients with moderate and 97 patients with severe RI to placebo. The group of patients with severe RI included four patients with end stage renal disease (ESRD) who required hemodialysis, two in each treatment group. Data from these patients are included, but not presented separately.

Table 1 summarizes the baseline demographic and background characteristics of patients, as well as baseline antidiabetic therapy. The baseline A1C was 7.7–7.8% in the two RI categories. The mean T2DM duration was 15.1 years for patients with moderate RI. More than 2/3 of these patients were treated with insulin at study entry with a mean dose of 56 U/day in both treatment groups. The patients with severe RI had a mean duration of T2DM of 18.1 years. More than 3/4 of patients were treated with insulin at study entry with mean doses of 53 and 50 IU/day in the vildagliptin and placebo treatment group, respectively. Overall, no major differences in demography or concomitant medications between treatment groups were observed.

Nearly all of the patients were receiving antihypertensive agents that block the renin-angiotensin-aldosterone system (RAAS), over half were receiving statins and approximately half were taking platelet aggregation inhibitors.

Patients with moderate or severe RI had previous or ongoing medical conditions common in the population with T2DM, with hypertension reported in more than 90% and dyslipidemia in more than 60% of randomized patients. No major differences between treatment groups were observed in the moderate RI group. However, in patients with severe RI, a nearly threefold higher percentage of patients randomized to vildagliptin than placebo had a history of infections (27.4 vs. 9.3%) and a nearly twofold higher percentage had a history of respiratory, thoracic and mediastinal disorders (21.0 vs. 12.4%).



*mild RI revealed during reclassification by MDRD method; 7 were randomized to vildagliptin, 3 to placebo, but data from mild RI patients are not reported. ATPR = abnormal test procedure result; ALV = abnormal laboratory value

Figure 1. Patient disposition.

Efficacy

Figure 2 depicts the time-course of mean A1C and the adjusted mean changes in A1C (AMΔ A1C) in patients with moderate (panels A and B) or severe (panels C and D) RI during the 24-week treatment. In patients with moderate RI receiving vildagliptin, the AMΔ A1C was $-0.7 \pm 0.1\%$ from a mean baseline of 7.9%, with a between-treatment difference of $-0.5 \pm 0.1\%$ ($p < 0.0001$). Of patients with moderate RI receiving vildagliptin, 30.2% achieved target A1C <7%, while 24.8% of those receiving placebo achieved target. This, however, did not reach statistical significance. Rescue therapy was given to 5% of patients receiving vildagliptin and 10% of patients receiving placebo.

In patients with severe RI receiving vildagliptin, the AMΔ A1C was $-0.9 \pm 0.2\%$ from a baseline of 7.7%, again with a highly-significant between-treatment difference of $-0.6 \pm 0.1\%$ ($p < 0.0001$). In patients with severe RI, a significantly higher percentage of patients receiving vildagliptin (48.3%) than placebo (25.0%) achieved target A1C <7% ($p = 0.003$). Rescue therapy was given to 1% of patients receiving vildagliptin and 3% of patients receiving placebo.

A clinically relevant decrease in FPG was seen with vildagliptin, both in patients with moderate (AMΔ $= -1.0 \pm 0.3$, from a baseline of 9.2 mmol/l) and severe (AMΔ $= -1.2 \pm 0.5$, from a baseline of 8.1 mmol/l) RI. However, the between-treatment difference was not statistically significant in either moderate (-0.5 ± 0.3 mmol/l, $p = 0.144$) or severe (-0.5 ± 0.4 mmol/l, $p = 0.185$) RI patients.

Safety

The overall safety and tolerability of vildagliptin 50 mg qd in patients with moderate or severe RI was generally similar to placebo, as reported in Table 2, which summarizes the incidences of AEs, serious adverse events (SAEs), discontinuations because of AEs and deaths by treatment and severity of RI. There was a trend towards a lower incidence of any AE with vildagliptin than with placebo in both moderate (67.5 vs. 72.9%) and severe (72.6 vs. 74.2%) RI. Overall there were no important differences between vildagliptin and placebo or appreciable trends in the incidence of SAEs in patients with moderate or severe RI, and the majority of SAEs were scattered across many different system organ classes (SOCs). The number of deaths were similar for vildagliptin and placebo (a total of 4 vs. 5 cases in the two RI categories). None of the deaths was suspected to be related to study drug.

Table 1. Baseline patient demographic and background characteristics and prior (ongoing) antidiabetic therapy.

	Moderate RI		Severe RI*	
Demographic variable Mean ± SD or n (%)	Vildagliptin 50 mg qd (n = 165)	Placebo (n = 129)	Vildagliptin 50 mg qd (n = 124)	Placebo (n = 97)
Age (years)	67.7 ± 8.8	69.7 ± 7.3	64.1 ± 9.2	64.5 ± 10.8
eGFR [MDRD (ml/min/1.73^2)]	39.3 ± 6.0	40.3 ± 5.8	21.9 ± 5.7	20.9 ± 6.4
Age group n (%)				
≥65 y	114 (69.1)	102 (79.1)	64 (51.6)	48 (49.5)
≥75 y	36 (21.8)	35 (27.1)	14 (11.3)	20 (20.6)
Sex male	96 (58.2)	80 (62.0)	65 (52.4)	53 (54.6)
Race; n (%)				
Europid	116 (70.3)	94 (72.9)	61 (49.2)	49 (50.4)
Asian (Indian subcontinent)	24 (14.5)	15 (11.6)	22 (17.7)	21 (21.6)
Asian (non-Indian subcontinent)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
Hispanic or latino	21 (12.7)	16 (12.4)	36 (29.0)	26 (26.8)
Black	2 (1.2)	0 (0.0)	2 (1.6)	0 (0.0)
Other	2 (1.2)	4 (3.1)	1 (0.8)	1 (1.0)
BMI (kg/m^2)	30.2 ± 5.1	30.0 ± 5.0	30.2 ± 5.6	29.5 ± 5.0
A1C (%)	7.8 ± 1.0	7.8 ± 0.9	7.7 ± 1.0	7.7 ± 1.0
≤8%	98 (59.4)	80 (62.0)	87 (70.2)	66 (68.0)
FPG (mmol/l)	9.1 ± 3.3	8.4 ± 2.7	8.1 ± 2.8	8.6 ± 3.4
Duration of T2DM (years)	15.0 ± 9.1	15.2 ± 10.0	17.3 ± 8.6	19.0 ± 9.6
Current antidiabetic therapy				
None	6 (3.6)	5 (3.9)	5 (4.0)	1 (1.0)
Any	159 (96.4)	124 (96.1)	119 (96.0)	96 (99.0)
Insulin monotherapy	95 (57.6)	68 (52.7)	87 (70.2)	66 (68.0)
Insulin & OAD	18 (10.9)	20 (15.5)	13 (10.5)	12 (12.4)
OAD monotherapy	39 (23.6)	33 (25.6)	18 (14.5)	14 (14.4)
OAD combination therapy	7 (4.2)	3 (2.3)	1 (0.8)	4 (4.1)

Demography and duration of T2DM was collected on day of screening (Week -2). Baseline A1C and FPG were collected on Day 1 or the sample obtained at an earlier visit closest to Day 1, if Day 1 measurement was missing. RI, renal impairment.
*Two patients in each treatment group had ESRD.

Table 3 summarizes the most common individual AEs (occurring in ≥5% of patients in any group). In general, the incidences of common AEs were similar between treatment groups both in moderate and severe RI. In patients with severe RI, the most notable between-treatment difference in any specific AE was hyperkalemia (10.5% with vildagliptin vs. 4.1% with placebo). However, none of the events were severe, suspected to be related to study drug or led to discontinuation. Of note, potassium levels fluctuated during the double-blind period, as is typical in this renally impaired population, and these were reported as AEs of hyperkalemia. The percentage of patients with a notable potassium elevation of ≥6 mmol/l during the study was similar with vildagliptin (13.8%) and placebo (11.6%).

In the moderate RI group, 17.2% of patients receiving vildagliptin experienced hypoglycemic events, and hypoglycemia was reported by 11.6% of patients receiving placebo. While the overall incidence of hypoglycemia was numerically somewhat higher with vildagliptin than placebo, the incidence of severe hypoglycemic events was 1.2% with vildagliptin versus 1.6% with placebo, with no discontinuations in either group. Notably, in elderly patients (aged ≥65 years) the percentage experiencing hypoglycemic events was similar in both groups (11.5% with vildagliptin and 11.8% with placebo). In patients with severe RI, the incidence of hypoglycemia was similar with vildagliptin (15.3%) and placebo (12.4%), as was the incidence of severe hypoglycemia (1.6 vs. 2.1%). The incidence of hypoglycemia in patients with severe RI aged ≥65 years was 15.6% with vildagliptin and 18.8% with placebo.

The analyses of specific safety topics revealed no relevant between-treatment differences in hepatic-, skin-, edema- or pancreatitis-related AEs. In patients with moderate RI, the incidences of hepatic-, skin-, edema- and pancreatitis-related AEs in vildagliptin-treated patients were 1.2, 4.9, 11.0 and 0.0%, respectively; in patients receiving placebo these were 0.8, 3.1, 10.1 and 0.0%, respectively. In patients with severe RI, the incidences of hepatic-, skin-, edema- and pancreatitis-related AEs in vildagliptin-treated patients were 0.8, 2.4, 16.9 and 0.0%, respectively; in patients receiving placebo these were 1.0, 6.2, 18.6 and 0.0%, respectively.

The incidence of AEs in the infections and infestations SOC in patients with moderate RI was similar for vildagliptin (23.3%) and placebo (27.1%). In patients with severe RI, the incidence of infections and infestations AEs was higher with vildagliptin than placebo (30.6 vs. 19.6%), contrary to what was observed in patients with moderate RI. Most of these AEs were mild or moderate, none was suspected to be related to study drug. The imbalance was largely driven by more cases of mild influenza on vildagliptin (6.5 vs. 1.0% on placebo). The higher percentage of patients on vildagliptin

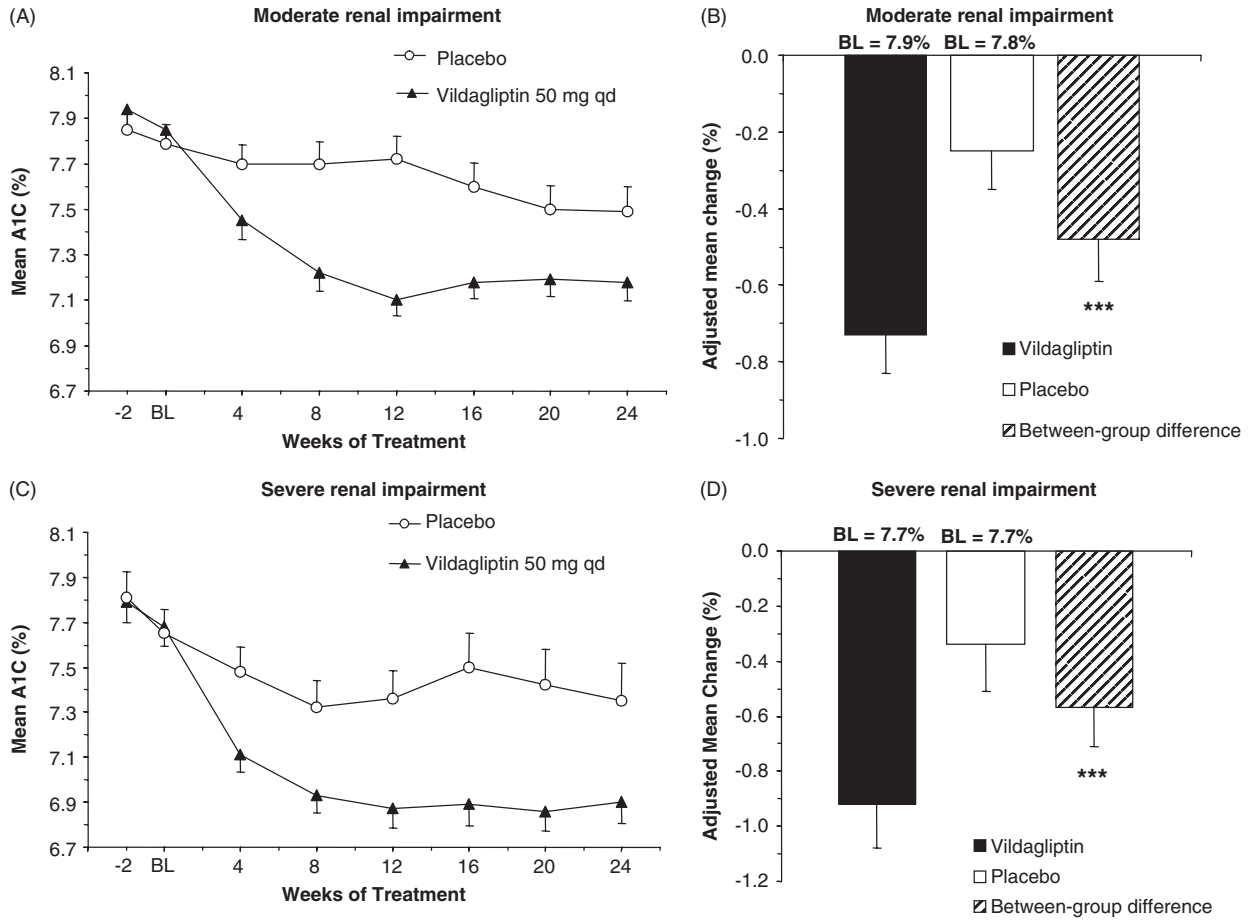


Figure 2. (A) Time-course of mean A1C during rescue-free treatment in patients with moderate renal impairment. Mean ± SE. n for vildagliptin group at baseline (BL) and Wk 24 = 158 and 133 patients, respectively; n for placebo group at BL and Wk 24 = 128 and 100, respectively. (B) Adjusted mean change from baseline to Wk 24 in patients with moderate RI receiving vildagliptin (closed bars, n = 157) or placebo (open bars, n = 128) and between-group difference (hatched bars). ***$p < 0.0001$. (C) Time-course of mean A1C during rescue-free treatment in patients with severe renal impairment. Mean ± SE. n for vildagliptin group at BL and Wk 24 = 123 and 103 patients, respectively. n for placebo group at BL and Wk 24 = 95 and 76 patients, respectively. (D) Adjusted mean change from baseline to Wk 24 in patients with severe RI receiving vildagliptin (closed bars, n = 122) or placebo (open bars, n = 95) and between-group difference (hatched bars). ***$p < 0.0001$.

with a medical history of infections and infestations, and in the respiratory, thoracic and mediastinal disorders SOC described under demography may also explain this finding since these events have a propensity to recur.

The rate of cardiac events (cardiac disorder SOC) was numerically lower with vildagliptin compared to placebo (4.9% with vildagliptin vs. 8.5% with placebo) in patients with moderate RI. The rate of cardiac events in the severe RI group was nearly identical with either treatment (vildagliptin, 12.1%; placebo, 12.4%).

No vildagliptin-treated patients with moderate or severe RI had treatment-emergent persistent elevation of ALT ≥3xULN. One vildagliptin patient with severe RI had a CPK elevation of 12 000 U/l. This clinically asymptomatic event occurred in

Table 2. Overall summary of adverse events by treatment and severity of renal impairment.

	Moderate RI [n (%)]		Severe RI [n (%)]	
Event category	Vildagliptin 50 mg qd (n = 163)	Placebo (n = 129)	Vildagliptin 50 mg qd (n = 124)	Placebo (n = 97)
Any AE	110 (67.5)	94 (72.9)	90 (72.6)	72 (74.2)
Any SAE	15 (9.2)	11 (8.5)	23 (18.5)	20 (20.6)
Any AE leading to discontinuation	4 (2.5)	7 (5.4)	11 (8.9)	6 (6.2)
Deaths	1 (0.6)	1 (0.8)	3 (2.4)	4 (4.1)

RI, renal impairment.

Table 3. Summary of common adverse events by treatment and severity of renal impairment.

	Moderate RI [n (%)]		Severe RI [n (%)]	
Preferred term (PT)	Vildagliptin 50 mg qd (n = 163)	Placebo (n = 129)	Vildagliptin 50 mg qd (n = 124)	Placebo (n = 97)
Common AEs (≥5% in any group, by PT)				
Asthenia	9 (5.5)	6 (4.7)	7 (5.6)	6 (6.2)
Back pain	3 (1.8)	5 (3.9)	1 (0.8)	5 (5.2)
Blood glucose decreased	13 (8.0)	4 (3.1)	7 (5.6)	3 (3.1)
Diarrhoea	8 (4.9)	5 (3.9)	11 (8.9)	8 (8.2)
Dizziness	14 (8.6)	14 (10.9)	12 (9.7)	10 (10.3)
Dyspnoea	2 (1.2)	2 (1.6)	4 (3.2)	5 (5.2)
Fatigue	6 (3.7)	3 (2.3)	7 (5.6)	2 (2.1)
Hyperhidrosis	12 (7.4)	12 (9.3)	13 (10.5)	8 (8.2)
Hyperkalemia	4 (2.5)	4 (3.1)	13 (10.5)	4 (4.1)
Hypertension	3 (1.8)	3 (2.3)	6 (4.8)	9 (9.3)
Hyperuricaemia	2 (1.2)	3 (2.3)	3 (2.4)	6 (6.2)
Hypoglycemia	28 (17.2)	15 (11.6)	19 (15.3)	12 (12.4)
Influenza	4 (2.5)	2 (1.6)	8 (6.5)	1 (1.0)
Nasopharyngitis	9 (5.5)	13 (10.1)	4 (3.2)	5 (5.2)
Nausea	5 (3.1)	4 (3.1)	7 (5.6)	6 (6.2)
Oedema peripheral	18 (11.0)	13 (10.1)	21 (16.9)	18 (18.6)
Tremor	11 (6.7)	10 (7.8)	6 (4.8)	1 (1.0)
Urinary tract infection	5 (3.1)	5 (3.9)	6 (4.8)	5 (5.2)
Vomiting	0 (0.0)	4 (3.1)	7 (5.6)	4 (4.1)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. Coded using MedDRA version 13.1. RI, renal impairment.

a patient who was treated with lovastatin at a dose twice that recommended for patients with severe RI. This patient also had a history of alcohol abuse and elevated CPK at baseline. CPK returned to normal values after discontinuation of vildagliptin and the statin.

There were no meaningful changes in renal function, as measured by potassium, creatinine and eGFR changes from baseline to study end, in either renal impairment group during this 24-week study.

Discussion

The present multi-centre, randomized, double-blind, placebo-controlled 24-week study was undertaken to assess the safety, tolerability and efficacy of vildagliptin (50 mg qd) added to ongoing antidiabetic therapy in patients with T2DM and moderate or severe RI. While DPP-4 inhibitors have been studied previously in patients with T2DM and moderate to severe RI, and no safety signals were identified for sitagliptin [10] or saxagliptin [9], the relatively small sample sizes (91 patients in the sitagliptin study and 170 patients in the saxagliptin study) and short duration (12 weeks) of the placebo-controlled study period of the prior studies limit conclusions regarding the safety of DPP-4 inhibitors in patients with T2DM and moderate or severe RI. The present, much larger, 24-week study of 515 patients with moderate or severe RI confirms the safety and demonstrates efficacy of the DPP-4 inhibitor vildagliptin added to ongoing antidiabetic therapy in this high-risk population. The incidences of any AE, any SAE, discontinuations because of AEs and deaths with vildagliptin were similar to those occurring in patients receiving placebo, both in those with moderate and those with severe RI.

Further, with regard to events that are of particular interest for vildagliptin or DPP-4 inhibitors in general, there was no signal related to hepatic-, skin- or pancreatitis-related safety associated with vildagliptin treatment. In severe RI patients, there were more events in the infections and infestations SOC with vildagliptin, which was mostly driven by a higher rate of mild events of influenza. This could be because of a higher background risk of recurrent infections based on their underlying medical history as presented earlier. There was no such finding in moderate RI patients, and also not in a recent analysis of pooled data from 12 000 patients [7].

Despite the increased CV vulnerability of patients with T2DM and renal impairment, there was no increased frequency of AEs in the cardiac disorders SOC, consistent with published data from patients with normal renal function or mild RI [5].

The present study therefore extends the good safety and tolerability profile of vildagliptin seen in patients with normal renal function or mild RI [5–7,14,15] to patients with moderate or severe RI. However, an obvious limitation of the present study is the low number of patients with ESRD requiring hemodialysis that were included, clearly limiting conclusions regarding vildagliptin safety and efficacy in such patients.

The efficacy of twice daily administration of 50 mg vildagliptin in patients with normal renal function results from its ability to completely block DPP-4-mediated inactivation of GLP-1 and GIP over a 24-h period, reducing postprandial glucose levels and also overnight endogenous glucose production [16]. This dose regimen in patients with T2DM and normal renal function or mild RI is not associated with treatment

emergent AEs [5–7,14] and is maximally efficacious [12,13]. Impaired renal function is not expected, nor has it been seen to increase the C_{max} of vildagliptin; rather, exposure to vildagliptin is increased by approximately twofold in patients with severe RI, reflecting an increase in the $T_{1/2}$. Accordingly, in patients with renal impairment, a single 50 mg dose is expected to maintain the 24-h DPP-4 blockade. This is supported by the A1C reductions seen in the present study, which are similar to the reductions observed with the vildagliptin 50 mg bid dose in a similar population with preserved renal function and a similar baseline A1C [12,17–19].

A1C levels can be influenced by renal disease or anti-anemic medications such as iron or erythropoietin. However, the placebo-controlled design of the present study and the fact that usage of anti-anemic medications was balanced across treatment groups support the conclusion that vildagliptin *per se* was responsible for the improved metabolic control indicated by reduced A1C relative to placebo.

Hypoglycemia is an important consideration in patients with moderate or severe RI, given that many factors contribute to hypoglycemia in that population, including treatment with insulin and SUs [20]. A slightly higher rate of hypoglycemia was seen in vildagliptin-treated patients with moderate RI, whereas in patients with severe RI, hypoglycemia rates were similar for vildagliptin and placebo. Importantly, the risk of severe hypoglycemia requiring third party help was low and similar to placebo in both patients with moderate and severe RI. This finding is particularly noteworthy given that vildagliptin-treated patients had tighter glycemic control as indicated by the lower A1C levels throughout the study, and the vast majority of patients were receiving insulin background therapy. The present findings are consistent with earlier reports that vildagliptin carries low risk of hypoglycemia when combined with insulin [17], presumably by improving the responsiveness of the pancreatic α-cells to low levels of glucose whilst suppressing inappropriate glucagon secretion during hyperglycemia, shown previously in patients with T2DM and normal renal function [21].

In summary, the present study is unprecedented in terms of number of patients with moderate or severe renal failure exposed to a DPP-4 inhibitor. Treatment with vildagliptin (50 mg qd) added to ongoing antidiabetic therapy was well-tolerated, with a safety profile comparable to placebo. Further, in patients with moderate or severe renal RI, vildagliptin added to current therapy elicited robust improvements in glycemic control, with A1C reductions of ~0.7% (from baseline 7.9% in moderate impairment) and ~0.9% (from baseline of 7.7% in severe impairment). Accordingly, it may be concluded that vildagliptin treatment is well-tolerated and effective in patients with T2DM and moderate or severe renal impairment.

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Conflict of Interest

V. L. was critical to conducting the trial, data collection and initial data interpretation, and drafting the manuscript. Q. S. was responsible for the statistical analysis. A. S. contributed to the initial data interpretation and was involved in drafting the manuscript. P.-H. G. represented the study investigators and contributed to the clinical interpretation of the data. W. K. contributed to study design, the initial data interpretation and overall clinical interpretation. All authors were involved in manuscript revisions and are responsible for intellectual content.

P.-H. G. has served on advisory boards for Novartis, Boehringer Ingelheim and Cebix, has received honoraria for speaking engagements from Novartis, Boehringer Ingelheim, Novo-Nordisk, Eli Lilly, Genzyme and MSD Finland and received research support from Eli Lilly. V. L., Q. S., A. S. and W. K. are employed by and own shares in Novartis.

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ORIGINAL ARTICLE

Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients

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Aims: To report the cardiovascular (CV) safety profile and heart failure (HF) risk of vildagliptin from a large pool of studies, including trials in high-risk patients with type 2 diabetes mellitus (T2DM), such as those with congestive HF and/or moderate/severe renal impairment.

Methods: We conducted a retrospective meta-analysis of prospectively adjudicated CV events. Patient-level data were pooled from 40 double-blind, randomized controlled phase III and IV vildagliptin studies. The primary endpoint was occurrence of major adverse CV events (MACEs; myocardial infarction, stroke and CV death). Assessments of the individual MACE components and HF events (requiring hospitalization or new onset) were secondary endpoints. The risk ratio (RR) of vildagliptin (50 mg once- and twice-daily combined) versus comparators (placebo and all non-vildagliptin treatments) was calculated using the Mantel–Haenszel (M–H) method.

Results: Of the 17 446 patients, 9599 received vildagliptin (9251.4 subject-years of exposure) and 7847 received comparators (7317.0 subject-years of exposure). The mean age of the patients was 57 years, body mass index 30.5 kg/m^2 (nearly 50% obese), glycated haemoglobin concentration 8.1% and T2DM duration 5.5 years. A MACE occurred in 83 (0.86%) vildagliptin-treated patients and 85 (1.20%) comparator-treated patients, with an M-H RR of 0.82 [95% confidence interval (CI) 0.61–1.11]. Similar RRs were observed for the individual events. Confirmed HF events were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients, with an M–H RR 1.08 (95% CI 0.68–1.70).

Conclusions: This large meta-analysis indicates that vildagliptin is not associated with an increased risk of adjudicated MACEs relative to comparators. Moreover, this analysis did not find a significant increased risk of HF in vildagliptin-treated patients.

Keywords: antidiabetic drug, cardiovascular disease, dipeptidyl peptidase-4 inhibitor, meta-analysis

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Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular (CV) diseases, such as myocardial infarction (MI) and stroke. Patients with T2DM have a two- to fourfold higher risk of CV disease and CV mortality compared with patients without T2DM [1,2]. In middle-aged adults, T2DM shortens life expectancy by 5–10 years, mainly as a result of an increase in CV mortality [3]; therefore, it is desirable that any antidiabetic treatment should lower this risk or at least not increase it.

Many antidiabetic agents are available for the treatment of T2DM; however, there are limited CV safety data from clinical trials for these agents, and there are concerns of increased CV risk with some drugs [4–6]. As a result, in 2008, the US Food and Drug Administration [7] and the European Committee for Medicinal Products for Human Use [8] issued new guidance regarding the assessment of CV safety of new antidiabetic medications, highlighting the need to more thoroughly address CV safety during the development of such drugs.

Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycaemic control with a low risk of hypoglycaemia in a wide range of patient populations [9]. Vildagliptin is widely used, with the cumulative patient exposure exceeding 10 million patient-years as of 2014 (data on file). Since a previous assessment of vildagliptin CV safety [10], many additional studies have been completed, including trials in high-risk patients such as those with heart failure (HF) or moderate/severe renal impairment, providing a more comprehensive data set. Furthermore, while three recently completed DPP-4 inhibitor CV outcome trials (SAVOR-TIMI-53 [11], EXAMINE [12] and TECOS [13]) confirmed the overall CV safety of saxagliptin, alogliptin and sitagliptin, respectively; SAVOR-TIMI-53 [11] reported that significantly more patients treated with saxagliptin were hospitalized for HF compared with placebo, triggering a debate about the safety of the DPP-4 inhibitor class with regard to HF. It was important, therefore, to re-assess the CV safety of vildagliptin in the enlarged pool of studies, including an assessment of HF risk, which had not been included in a previous meta-analysis [10].

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Materials and Methods

Study Design

The CV safety profile of vildagliptin was assessed by a meta-analysis of randomized, double-blind, controlled (active or placebo) phase III and IV studies, at vildagliptin doses ≥50 mg daily and for at least 12 weeks' duration (up to >104 weeks). The phase II studies were not included because independent adjudication was performed for phase III and IV studies only. Patient-level data from all studies completed as of December 2013 were pooled in the present analysis. This included data from 40 monotherapy and combination therapy trials, all of which studied the glucose-lowering effects of vildagliptin in patients with T2DM or, in one study, those with impaired glucose tolerance. Thirty-seven of these trials included the two registered doses of vildagliptin (50 mg once daily and 50 mg twice daily), whereas three trials studied the non-registered 100 mg once-daily dose. Details of the study design of the contributing studies [14–57] are summarized in Table S1 and are also provided in the individual study publications.

For the demographic/baseline characteristics and patient exposure, the comparator group included pooled safety data from the comparator arms of all 40 vildagliptin studies. Safety data are presented for the approved dose (i.e. vildagliptin 50 mg once daily and twice daily) and all the studied doses (including the vildagliptin 100 mg once-daily dose) separately. For the former, the comparison of risk ratios (RRs) was made against comparator data from those 37 trials in which vildagliptin 50 mg once daily and/or 50 mg twice daily were studied. These data are presented in the main paper. Key analyses of RRs of vildagliptin versus comparators, including the non-registered 100 mg once-daily dose (i.e. from all 40 studies) are shown for completeness in Table S2. The results of all the vildagliptin doses (50 mg once daily/50 mg twice daily/100 mg once daily) were consistent with the data from the main analyses, with the registered vildagliptin 50 mg once-daily/twice-daily doses.

Study Endpoints and Assessments

The primary CV endpoint was a composite of major adverse CV events (MACEs) consisting of adjudicated non-fatal MI, non-fatal stroke and CV death. Individual components of the primary composite endpoint, the composite of any adjudicated CV events and all-cause mortality and adjudicated HF events (new onset or hospitalization for worsening HF) were assessed as secondary endpoints.

All adverse events (AEs) were recorded and assessed by the study investigator(s) with respect to their severity and possible relationship with the study medication. An independent adjudication committee, comprising five cardiologists and one neurologist who otherwise did not participate in the trials, was in place during the conduct of the phase III and IV studies. The adjudication committee prospectively reviewed all CV events in a blinded and pre-planned fashion. Only CV events adjudicated as 'confirmed' by the adjudication committee were included in the analyses. A classification of adjudicated CV events by category and diagnosis is provided in Table S3.

Statistical Analysis

The RR and its 95% confidence interval (CI) of patients with MACEs in the vildagliptin group [registered doses of 50 mg once daily/twice daily (main paper) or all vildagliptin (50 mg once daily/50 mg twice daily/100 mg once daily); Table S2] versus the comparators group were combined across studies with at least one event using a Mantel–Haenszel (M–H) method. Such an analysis was also performed using subgroups of age (<65 and ≥65 years), gender and CV risk status [high CV-risk status defined as a history of events in the Standard Medical Dictionary for Regulatory Activities Queries (SMQs) of 'ischaemic heart disease, cardiac failure, ischaemic cerebrovascular conditions and/or embolic/thrombotic events, arterial', or 'two or more concomitant CV risk factors of age ≥60 years (females) or 55 years (males) plus either hypertension and/or dyslipidaemia'], as well as in the subset of long-term studies with a duration of ≥52 weeks. Tests for heterogeneity across studies and by subgroups were assessed using the Cochrane's Q-test, using $p \leq 0.1$ as indicative of significant heterogeneity, and the scale-free I^2 index representing the percentage of variability across trials attributable to heterogeneity rather than chance.

The M–H RR and 95% CI were also provided for the individual components of the MACE endpoint, for the secondary composite endpoint of any adjudicated CV events and all-cause mortality, and for the endpoint of adjudicated worsening HF requiring hospitalization or new-onset of HF. Patient demographics, baseline characteristics and CV history were analysed using descriptive statistics.

Ethics and Good Clinical Practice

All studies contributing to this meta-analysis were conducted in accordance with good clinical practice and the Declaration of Helsinki. All study protocols were approved by the relevant independent ethics committee/institutional review board. All patients from each study provided written informed consent.

Results

Exposure

A total of 9599 patients (9251.4 subject-years of exposure) received vildagliptin 50 mg once daily (n = 2201) or vildagliptin 50 mg twice daily (n = 7398) and 7847 patients (7317.0 subject-years of exposure) were exposed to a comparator. The mean duration of exposure was 50.3 weeks for vildagliptin compared with 48.7 weeks for comparators. The comparator group consisted of 36% placebo, 33% sulphonylurea, 10% thiazolidinediones, 15% metformin and 6% other treatments (mostly α-glucosidase inhibitors).

Baseline Characteristics and Demographics

Patient demographics and baseline characteristics were similar in the vildagliptin and comparator groups (Table 1). Overall, the mean age of patients was 57 years, with 27% of patients aged ≥65 years. The mean body mass index was 30.5 kg/m^2; nearly half of the patients were obese (≥30 kg/m^2), with ~20% being morbidly obese (≥35 kg/m^2). Glycated haemoglobin was

Table 1. Patient demographics, baseline characteristics and cardiovascular history.

Variable	Vildagliptin 50 mg once daily/twice daily (N = 9599)	Comparators (N = 7847)
Mean ± s.d. age, years	56.5 ± 10.9	57.6 ± 10.8
Elderly (≥65 years), n (%)	2360 (24.6)	2279 (29.0)
Gender, n (%)		
Male	5310 (55.3)	4304 (54.8)
Female	4289 (44.7)	3543 (45.2)
Race, n (%)		
White	6043 (63.0)	4935 (62.9)
Asian	2165 (22.6)	1688 (21.5)
Hispanic or Latino	929 (9.7)	867 (11.0)
Black	343 (3.6)	238 (3.0)
All other	119 (1.2)	119 (1.5)
Mean ± s.d. body weight, kg	85.1 ± 18.9	84.5 ± 18.9
Mean ± s.d. BMI, kg/m^2	30.5 ± 5.5	30.4 ± 5.5
BMI ≥30 kg/m^2, n (%)	4679 (48.7)	3743 (47.7)
BMI ≥35 kg/m^2, n (%)	2039 (21.2)	1580 (20.1)
Mean ± s.d. HbA1c, %	8.2 ± 1.1	8.0 ± 1.1
Mean ± s.d. FPG, mmol/l	9.8 ± 2.7	9.6 ± 2.7
Mean ± s.d. T2DM duration (years)	5.3 ± 6.2	5.9 ± 6.5
≥5 to <10 years, n (%)	1995 (20.8)	1823 (23.2)
≥10 years, n (%)	1610 (16.8)	1473 (18.8)
Hypertension, n (%)	5436 (56.6)	4721 (60.2)
Dyslipidaemia, n (%)	4435 (46.2)	3631 (46.3)
Renal impairment, n (%)*	3961 (41.3)	3263 (41.6)
Mild (≥50 to ≤80)	3350 (34.9)	2766 (35.2)
Moderate (≥30 to <50)	391 (4.1)	328 (4.2)
Severe (<30)	220 (2.3)	169 (2.2)
Previous CV event history, n (%)†	1693 (17.6)	1415 (18.0)
High CV-risk status, n (%)*,‡	4432 (46.2)	3904 (49.8)
CV medications at baseline, n (%)		
Antihypertensives	5052 (52.6)	4424 (56.4)
RAS blocker	3997 (79.1)	3575 (80.8)
Diuretics	1373 (14.3)	1169 (14.9)
β-blockers	1763 (18.4)	1512 (19.3)
Lipid lowering medications, n (%)	3000 (31.3)	2622 (33.4)
Statins, n (%)	2648 (27.6)	2268 (28.9)
Platelet aggregation inhibitors, n (%)	2127 (22.2)	1848 (23.6)

BMI, body mass index; CV, cardiovascular; CCV, cardiovascular and cerebrovascular; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; MDRD, modification of diet in renal disease; RAS, renin-angiotensin system ; SMQs, Standard Medical Dictionary for Regulatory Activities Queries; T2DM, type 2 diabetes mellitus. Hypertension includes patients with a history of events in the SMQ 'Hypertension'; dyslipidaemia includes patients with a history of events in the SMQ 'Dyslipidaemia'.

*GFR (MDRD) ≤80 ml/min per 1.73 m^2.

†History of CV events in SMQs of 'ischaemic heart disease, cardiac failure, ischaemic cerebrovascular conditions and/or embolic thrombotic events, arterial'.

‡History of CV events or at least two CV risk factors.

8.1% and the mean duration of T2DM was ~5.5 years, with almost 40% of patients having long-standing (≥5 years) T2DM. CV risk factors were similar in both groups. Across both the groups, 46% of patients had dyslipidaemia and nearly 60% of patients had hypertension. The percentages of patients with renal impairment were similar in both the groups (vildagliptin, 41.3%; comparators, 41.6%). Approximately 18% of patients had a history of CV disease and nearly 50% of patients were considered to have a high CV-risk status (history of CV disease or at least two risk factors as defined above).

Approximately 55% of patients in the vildagliptin group and ~65% of those in the comparator group were receiving background antidiabetes medications at baseline. In both the groups, a vast majority (nearly 90%) of patients were on monotherapy treatment, mainly with metformin (67 and 74% in the vildagliptin and comparator groups, respectively); the other monotherapies were sulphonylureas (>10%), insulin (>10%) and, least frequently, thiazolidinediones. The most common background combination therapies were dual therapy with metformin and sulphonylurea or metformin and insulin.

The use of CV medications such as lipid-lowering agents and platelet aggregation inhibitors was similar between the vildagliptin and comparator groups at baseline (Table 1).

Adjudicated Analyses

Adjudicated MACEs. There were 96 CV events submitted for the vildagliptin group, of these 93 events (96.9%) were confirmed with assignment of a corresponding classification. In the comparator group, 96 CV events were submitted for review, of these, 95 events (99.0%) were confirmed with assignment of a corresponding classification.

The incidences and risk ratios for the MACE composite endpoint (MI, stroke and CV death) as well as the individual components are shown in Figure 1A. A MACE occurred in 83 (0.86%) patients receiving vildagliptin and 85 (1.20%) patients receiving comparators. The resulting M–H RR was 0.82 (95% CI 0.61–1.11). A statistical heterogeneity analysis (Q-test and I^2 index) showed a consistency in effects across the individual studies contributing to this result ($Q = 6.75$, $p = 0.999$ and $I^2 = 0.00$). The Kaplan–Meier estimates for the adjudicated composite endpoint of MACE in the vildagliptin and comparator groups are provided in Figure 1B. Similar M–H RRs were also observed for each individual component of the composite endpoint, with the RR for CV death being 0.77 (95% CI 0.45–1.31).

The results of an analysis of RRs for MACE in different subgroups are shown in Figure 2. The subgroups were defined by gender (male or female), age (<65 and ≥65 years of age) and high CV-risk status (yes or no; as detailed above). As would be expected, the highest incidence of adjudicated CV events was found in male patients (vildagliptin, 1.1%; comparators, 1.6%), patients aged ≥65 years (vildagliptin, 1.9%; comparators, 1.8%) and patients with a high CV-risk status (vildagliptin, 1.4%; comparator, 2.0%).

Results for the MACE composite endpoint across all of these subgroups (M–H RRs, 0.63–1.09) were consistent with the overall population, and no significant differences were detected.

An analysis of MACEs was also performed in the subset of long-term studies (≥52 weeks; mean duration of exposure ~18.5 months; n = 4391 for vildagliptin and n = 3836 for comparators). The M–H RR of the composite MACE endpoint for vildagliptin versus comparators in these long-term studies was 0.93 (95% CI 0.66–1.30; Figure 2), further strengthening the above conclusions from the overall population.

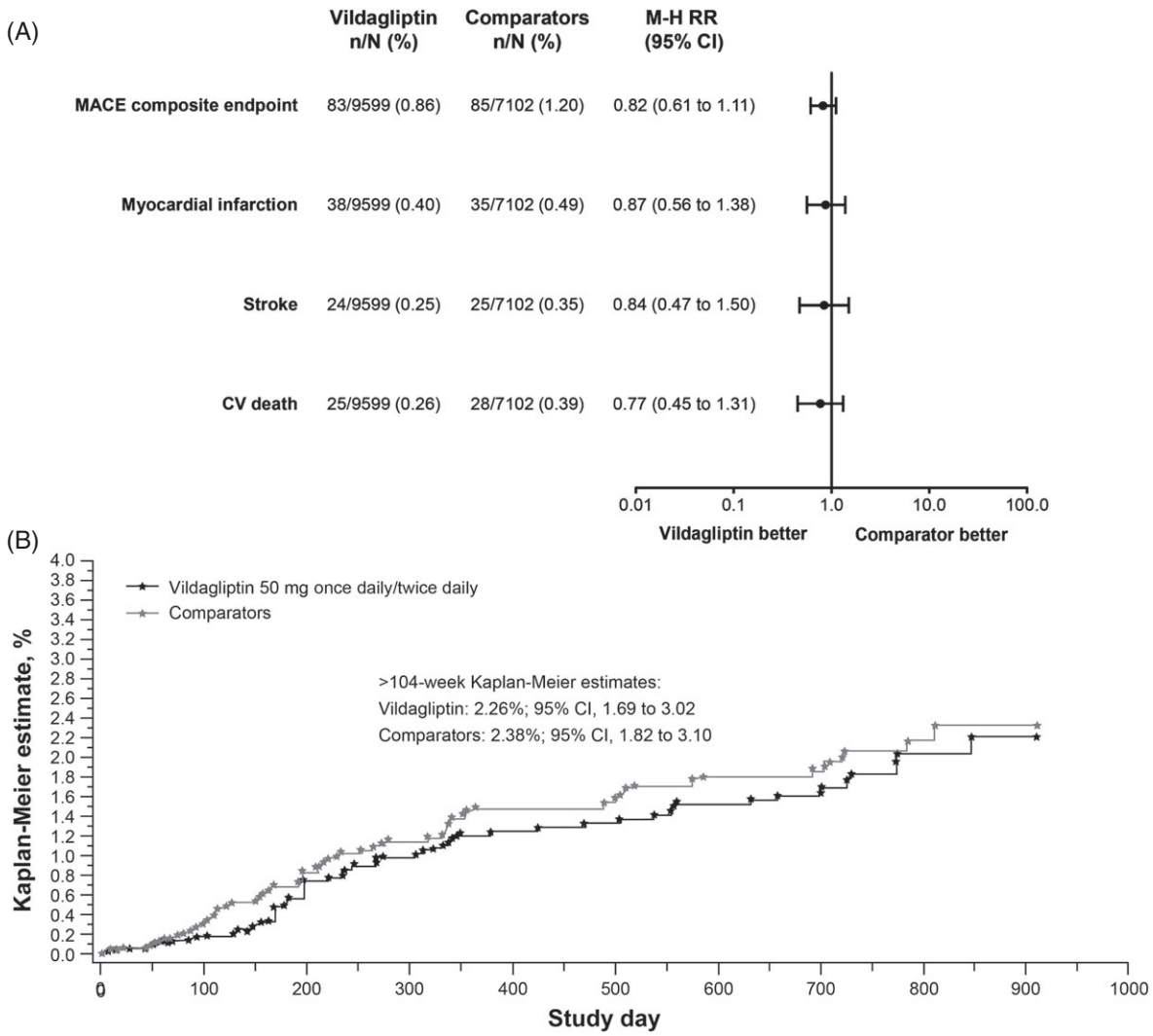

Figure 1. (A) Incidence and risk ratios for adjudicated composite endpoint of major adverse cardiovasular (CV) events (MACEs; consisting of myocardial infarction, stroke and CV death) and its individual components with vildagliptin (50 mg once daily/twice daily) versus comparators (placebo and active comparators). (B) Kaplan–Meier estimates (%) for the adjudicated composite endpoint of MACEs. CI, confidence interval; M–H RR, Mantel–Haenszel risk ratio.

Adjudicated Cardiovascular (Any) Events and All-Cause Mortality. A composite endpoint of any adjudicated CV events and all-cause mortality was also assessed. There was also no increased risk with vildagliptin (2.7%) versus comparators (3.3%) for this broader composite endpoint, with an M–H RR of 0.91 (95% CI 0.77–1.08).

Heart Failure Events

The HF endpoint included adjudicated events of HF requiring hospitalization or new onset of HF. Confirmed HF events were reported in 41 patients (0.43%) in the vildagliptin group and in 32 (0.45%) patients in the comparator group. In the vildagliptin group, five of the patients (0.1%) had a new onset of HF and 36 (0.4%) patients were hospitalized for worsening of HF. The same distribution was observed for the comparator group (0.1 and 0.4%, respectively). The incidences of adjudicated HF events were not significantly different between the vildagliptin and comparators, with an M–H RR of 1.08 (95% CI 0.68–1.70).

Discussion

The results of this retrospective meta-analysis of CV events, prospectively assessed by an independent and blinded expert adjudication committee, provided no indication of increased risk, including risk of HF, with vildagliptin compared with comparators. This meta-analysis included patient-level data from >17 000 patients from 40 phase III and IV studies. The patient population was representative of the broader T2DM population, but also included a significant number of patients who were at high CV risk. Approximately 50% of the study population had a medical history of CV events or two or more concomitant risk factors such as age ≥60 years (women) or ≥55 years (men) plus hypertension and/or dyslipidaemia. The

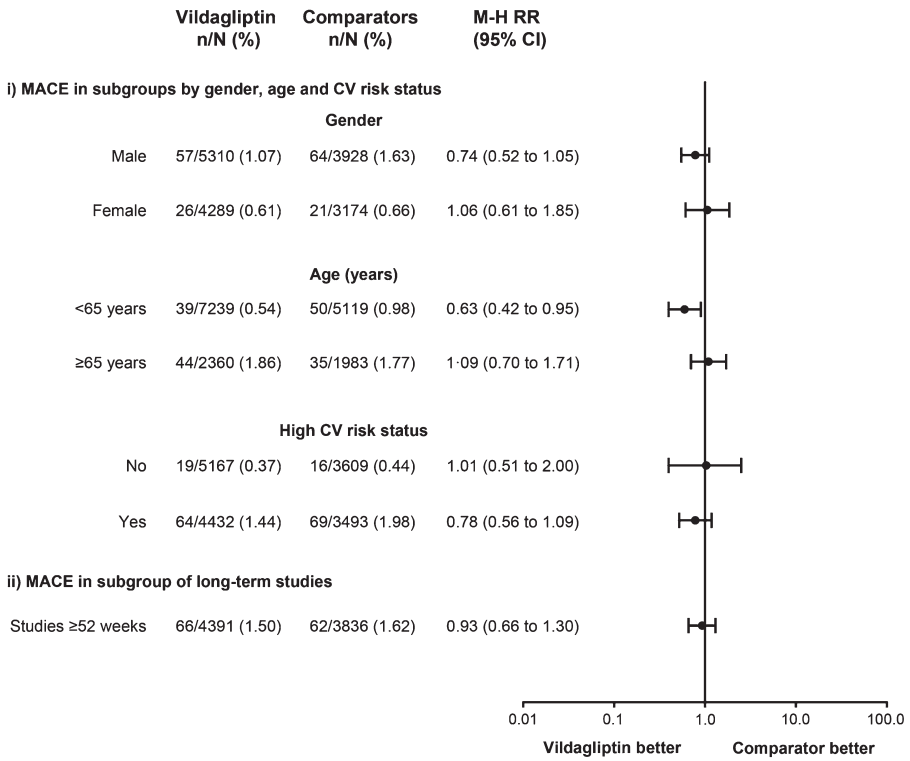

Figure 2. Incidences and risk ratios for adjudicated cardiovasular (CV) events with vildagliptin (50 mg once daily/twice daily) versus all comparators (placebo and active comparators) for: (i) major adverse CV events (MACEs; consisting of myocardial infarction, stroke and CV death) in subgroups based on gender, age (< and ≥65 years) and high CV-risk status[a]; (ii) MACEs in the subgroup of long-term studies (≥52 weeks). CI, confidence interval; M-H RR, Mantel-Haenszel risk ratio.

[a]High CV-risk status 'yes' includes patients with a history of events in the Standard Medical Dictionary for Regulatory Activities Queries of 'ischaemic heart disease, cardiac failure, ischaemic cerebrovascular conditions and/or embolic/thrombotic events, arterial', or 'two or more concomitant CV risk factors of age ≥60 years (females) or 55 years (males) plus either hypertension and/or dyslipidaemia'.

study population also included patients from dedicated studies, with very high CV risk, such as HF or moderate/severe renal impairment. The relative risk (vildagliptin versus comparators) for the primary endpoint (MACEs) was 0.82, with a 95% CI that excludes an increased risk of >11%. This finding is in line with the results from a previous analysis of CV safety with vildagliptin using a smaller database [10]. Studies involving other DPP-4 inhibitors also showed a reduced risk of MACEs [58,59] which, in some instances, reached statistical significance [60–62]; however, the contributing studies were relatively short and not designed to assess CV outcomes, and therefore do not allow any conclusions to be drawn about CV benefits.

An analysis of subgroups of patients according to gender, CV risk status and age provided results consistent with those of the overall population. Similar results were derived from the subset of studies with duration of at least 52 weeks, supporting the conclusion that vildagliptin does not increase CV risk. In the high CV-risk subgroup (history of CV events or at least two CV risk factors) with consequent higher event rate during follow-up, relative risk was again less than unity (0.78) with an upper 95% CI that excludes a risk of >9%. This subgroup is similar to the patient populations studied in the recently completed SAVOR-TIMI-53 trial [11] and the TECOS study [13]. Both studies were large, prospective, relatively short-term, non-inferiority CV outcome trials comparing either saxagliptin or sitagliptin to placebo. Both trials provided no evidence of a clinically significant increased risk of the composite endpoint of CV death, MI or ischaemic stroke compared with placebo, with a hazard ratio (HR) close to 1.0, which is consistent with the findings from our current meta-analysis. Similar results were also reported with alogliptin in the EXAMINE trial [12] in an even higher risk population of patients who had a history of acute coronary syndrome.

In the SAVOR-TIMI-53 trial [11], significantly more patients receiving saxagliptin were hospitalized because of HF compared with placebo-treated patients (HR 1.27; 95% CI 1.07–1.51). This finding was supported by observational data with sitagliptin [63] and a recent meta-analysis [64] which also suggest an increased risk of hospitalization for HF associated with DPP-4 inhibitor therapy. In contrast, there was no significant increase in risk of hospitalization as a result of HF with alogliptin in the EXAMINE trial (HR 1.07; 95% CI 0.79–1.46) [65]. A recent population-based study also did not find an increased risk of congestive HF with incretin therapy (adjusted OR 0.85; 95% CI 0.62–1.16) [66].

The risk of worsening HF with the use of DPP-4 inhibitors is highly topical [67]. The rate encountered with vildagliptin in this meta-analysis (RR 1.08) is similar to that reported for

alogliptin in recently published HF data from the CV outcome EXAMINE study (HR 1.07) [65] and less than that reported for saxagliptin (HR 1.27) [11], and sitagliptin (adjusted odds ratio 1.84) in a retrospective analysis of insurance claims [63], and also less than that found in a retrospective analysis of different DPP-4 inhibitors (RR 1.16) [68]. It is important to note that the recently completed TECOS trial reported an HR of 1.00 for HF hospitalization [13]. This is particularly reassuring, because that study had a longer follow-up time than SAVOR-TIMI-53, with a median of 3 years. In our analysis, the event rates for new onset of HF or HF hospitalization in the vildagliptin (0.4%) and comparator groups (0.4%) were relatively low and similar. Consequently, the 95% CI or the relative risk was relatively wide. Nonetheless, the upper boundary (1.70) was similar to that in the outcome trials with many more events [11,65]; thus, the present meta-analysis identified no signal of increased risk of HF in patients treated with vildagliptin, although the event number is too small to either refute or confirm such a risk. Because of this small number of HF events, no further subgroup analyses of HF risk (i.e. in patients with high CV risk or obesity) were performed. Our findings are also consistent with data reported in a dedicated trial evaluating the effect of vildagliptin versus placebo in patients with T2DM and congestive HF (New York Heart Association classification I–III) [56,57]. In that study, left ventricular ejection fraction improved slightly in patients treated with vildagliptin or placebo, with no significant between-treatment difference; however, vildagliptin-treated patients had a small increase in left ventricular end-diastolic volume. The underlying mechanism or relevance of this finding is unclear. The study also reported a reduction in brain natriuretic peptide [56,57] that would speak against a detrimental effect of vildagliptin on the heart [69].

A key strength of the present analysis is that it included more patients with advanced renal impairment or CV disease history, including HF, than previous similar analyses; however, it also had several limitations. The analysis was not prespecified, but crucially the data included were adjudicated independently and prospectively in a blinded fashion, and the primary MACE endpoint is standard when assessing CV safety. The event rate in the study was lower relative to the reported CV outcome studies [11–13] but the 95% CIs for the primary and most secondary outcomes were relatively narrow, supporting the precision of the comparison. The study population was more representative of a general diabetes population with a lower risk of experiencing CV events compared with the SAVOR-TIMI-53 or TECOS trials and even more so, the EXAMINE trial. Hence, these findings may be more applicable to a real-life setting, although the mean age of our population was relatively young and the mean duration of diabetes was relatively short, which may limit the extrapolation of these data to very elderly patients. Many studies included in the meta-analysis were of short duration, but the average length of treatment of ~1 year is little different from the median duration of treatment in the SAVOR-TIMI-53 (2.1 years) [11] and EXAMINE trials (18 months) [12]. Although the CV outcome trials with glucose-lowering drugs have been criticised because of the short duration of treatment [70], the Kaplan–Meier curves for HF hospitalization in the SAVOR-TIMI-53 and EXAMINE trials showed complete separation at 360 days [11,12].

This meta-analysis of an enriched study population of >17 000 patients with a significant proportion of patients at increased CV risk provides reassurance for the continued role of vildagliptin in the treatment of T2DM. This is consistent with recently completed DPP-4 inhibitor CV outcome studies which supported the CV safety profile of the DPP-4 inhibitor class. There is still some uncertainty with regard to HF safety, although the data from the recently completed TECOS study are reassuring.

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Conflict of Interest

All authors have completed the ICMJE uniform disclosure form. G. M. reports personal fees from Novartis and Takeda Pharmaceuticals, outside the submitted work. M. E. reports personal fees from Novartis and Takeda Pharmaceuticals, and personal fees and other (research award) from Novo Nordisk and Sanofi, outside the submitted work. S. D. P. reports grants and personal fees from Novartis (during the conduct of the study), Merck Sharp & Dohme, Novo Nordisk and Takeda Pharmaceuticals, personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly & Co., GlaxoSmithKline, Hamni Pharmaceuticals, Intarcia Therapeutics Inc., Janssen Pharmaceuticals and Sanofi, outside the submitted work. M. S. reports personal fees from Novartis, Boehringer Ingelheim, Janssen Pharmaceuticals, Merck Sharp & Dohme and Bristol-Myers Squibb, outside the submitted work. A. S., V. L., Q. S., and W. K. are employed by and own shares in Novartis. This work was funded by Novartis Pharma AG.

All authors participated in the study design, data review and data interpretation. All authors were involved in manuscript outline and revisions and are responsible for intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Vildagliptin studies contributing to meta-analysis.

Table S2. Incidences and risk ratios for adjudicated composite endpoint of major adverse cardiovascular (CV) events (MACEs), individual MACE components, composite endpoint of any adjudicated CV events and all-cause mortality, and heart failure with vildagliptin (50 mg once daily/50 mg twice daily/100 mg once daily) versus comparators.

Table S3. Classification of adjudicated cardiovascular (CV) events by category and diagnosis.

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Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin

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Aim: To compare the tolerability and efficacy of vildagliptin to pioglitazone as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy over 1-year duration.
Methods: This 52-week, multicentre, randomized, active-controlled study compared vildagliptin (50 mg b.i.d., n = 295) and pioglitazone (30 mg daily, n = 281) in patients with inadequate glycaemic control [haemoglobin A1c (HbA_{1c}) 7.5–11%] receiving a stable dose of metformin (≥1500 mg). The primary objective was to demonstrate non-inferiority of vildagliptin at 24 weeks in the change in HbA_{1c} from baseline. The objective of the additional 28 weeks of the study was to assess long-term safety, while also assessing mean change from baseline to study end in HbA_{1c}, fasting plasma glucose and body weight.
Results: When added to a stable dose of metformin (mean baseline dose approximately 2 g/day), the non-inferiority of HbA_{1c} lowering of vildagliptin to pioglitazone over 24 weeks was established at the non-inferiority margin of 0.3% (between-group difference = 0.1%). During the remaining 28 weeks, comparable HbA_{1c} decreases were recorded in both groups. Overall adverse event (AE) rates were similar in both groups, as was the occurrence of peripheral oedema. Hypoglycaemia occurred rarely in both groups. Serious AEs occurred more frequently with pioglitazone group. While mean body weight increased significantly in the pioglitazone group (+2.6 kg) from baseline, there was no significant weight gain with vildagliptin (+0.2 kg).
Conclusions: When added to metformin, vildagliptin demonstrates favourable safety and tolerability over 1 year. Vildagliptin provided additional HbA_{1c} lowering to that achieved with metformin alone and comparable to that achieved with pioglitazone, with only pioglitazone causing weight gain.

Keywords: add-on therapy, efficacy, metformin, pioglitazone, safety, vildagliptin
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Introduction

The use of metformin as first-line treatment for type 2 diabetes, in conjunction with lifestyle intervention, is well established. When additional therapy is required to reach or maintain glycosylated haemoglobin A1c (HbA_{1c}) <7%, guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend the addition of insulin, a sulphonylurea, or a thiazolidinedione (TZD) [1]. Nevertheless, overall control of diabetes remains suboptimal with evidence suggesting that up to 65% of patients fail to meet target HbA_{1c} levels [2].

Despite their efficacy in lowering HbA_{1c}, TZDs are known to be associated with weight gain [3], oedema [3], decreases in bone mineral density [4] and an

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increased risk of heart failure [5]. Moreover, a recent study suggests that the TZD rosiglitazone may lead to an increased risk of myocardial infarction and cardiovascular-related mortality [6]. This study has prompted a consensus statement from the American Diabetes Association and European Association for the Study of Diabetes, which concluded that TZDs remain a second-line option, but physicians should exercise greater caution when considering such treatment [7]. Given these considerations, there remains a substantial unmet need for an oral antidiabetic drug that is safe, effective and well tolerated when added to metformin monotherapy.

Vildagliptin, a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycaemic control in patients with type 2 diabetes mellitus by increasing α- and β-cell responsiveness to glucose, is now approved in Europe as an add-on therapy to metformin, sulphonylurea or TZD. In large-scale clinical trials, vildagliptin (as monotherapy or in combination with other oral antidiabetic agents) has been shown to lower blood glucose levels [8,9] and significantly reduce HbA_{1c} while being well tolerated [10–12]. Mechanistic studies have suggested that DPP-4 inhibitors, such as vildagliptin, may be particularly effective when used in combination with metformin because of a synergistic effect in raising plasma levels of active glucagon-like peptide-1 [13,14].

Studies are ongoing to compare vildagliptin with a sulfonylurea as add-on to metformin, but here, we report data from a 52-week study comparing vildagliptin with pioglitazone as add-on treatment in patients with type 2 diabetes not achieving HbA_{1c} goal on metformin alone. The primary objective of this study was to demonstrate non-inferiority in glucose lowering of vildagliptin to pioglitazone at 24 weeks; these results have been reported previously [15]. After completion of 24 weeks, the study continued for a further 28 weeks to assess the long-term safety profiles of the two agents. This report focuses on the data from 52 weeks.

Methods

Study Design

This was a 52-week, two-part study consisting of a 24-week, double-blind, randomized, active-comparator phase, followed by a 28-week, single-blind, active-comparator phase, during which both the patients and the investigators remained fully blinded, while the sponsors (because of unblinding at 24 weeks) did not. Full details of the 24-week part of the study have been published previously [15]. Treatment assignment was through an automated central telephone system. Randomization numbers were generated to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A randomization number was assigned to each patient, which was used to link patients to one of the two treatment arms and specified a unique medication number for the first package of study drug to be dispensed to the patient. There was no stratification.

Patients with type 2 diabetes and a baseline HbA_{1c} of 7.5–11.0% receiving a stable dose of metformin ≥1500 mg/day were randomized to receive vildagliptin (50 mg b.i.d.) or pioglitazone (30 mg q.d.) as add-on treatment. Patients who completed the first 24 weeks of the study continued to receive assigned treatment for a further 28 weeks. Scheduled visits occurred at week −4, baseline, at weeks 4, 12, 16 and 24 (during the first 24 weeks of the study) and then at weeks 32, 40 and 52.

The study was conducted in accordance with the Declaration of Helsinki; the protocol was approved by the relevant ethics/approval committees. Informed consent was obtained from each patient in writing before study entry.

Study Population

Men and women (aged 18–77 years, fertile women were required to be using a medically approved method of birth control) with type 2 diabetes were eligible to participate if they had an HbA_{1c} of 7.5–11.0%, a fasting plasma glucose (FPG) of <15 mmol/l and a body mass index (BMI) of 22–45 kg/m^2.

Patients were excluded if any of the following key criteria applied: acute metabolic complications of diabetes; use of any other oral antidiabetic (other than metformin) in the 3 months before visit 1; chronic insulin treatment (>4 weeks of treatment in the absence of a intercurrent illness) within the past 6 months; myocardial infarction, unstable angina or coronary artery bypass surgery within previous 6 months; congestive heart failure (all New York Heart Association classes I–IV); liver disease; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN); bilirubin >1.3 times ULN; serum creatinine levels of ≥132 μmol/l (men) or ≥125 μmol/l (women); clinically significant abnormal thyroid-stimulating hormone; or fasting triglycerides >7.9 mmol/l.

Assessments

Assessments included HbA_{1c}, FPG, body weight and vital signs measured at all visits. Ankle circumference measurements to assess occurrence of peripheral oedema were taken at each visit postscreening. Standard

laboratory assessments were performed at each visit except at weeks 16 and 32. ECGs were performed at screening, baseline and weeks 12, 24 and 52.

All adverse events (AEs) were recorded and assessed for severity and possible relationship to study medication at each postbaseline visit. Patients were provided with glucose monitoring devices, and hypoglycaemia (regardless of severity) was defined as symptoms suggestive of low glucose confirmed by self-monitored glucose measurement of <3.1 mmol/l. Severe hypoglycaemia was defined as any episode requiring assistance of a third party. Selected clinical events were reviewed by independent adjudication committees.

Laboratory assessments were made by a central laboratory (Covance-US, Indianapolis, IN, USA). HbA_{1c} was measured with an ion-exchange high-performance liquid chromatography method, and all assays were performed with standardized and validated procedures according to good laboratory practice.

Statistical Analyses

The primary objective of the study was to demonstrate non-inferiority of vildagliptin to pioglitazone at 24 weeks, which was established if the upper limit of the 95% CI for the between-group difference in HbA_{1c} was $\leq$0.4%. Furthermore, if non-inferiority at the 0.4% margin was established, non-inferiority was also tested at the 0.3% level. These results have been previously reported [15] but are included within this report for completeness. A secondary objective was assessment of the long-term safety of vildagliptin at 52 weeks. Exploratory objectives included change from baseline in HbA_{1c}, FPG and body weight at 52 weeks. Descriptive statistics are presented for efficacy assessments at week 52, where *t* tests for the change from baseline at endpoint were performed within each treatment group, and AEs are summarized. All analyses were preplanned with the exception of the assessment of body weight changes in BMI-based subgroups.

The intent-to-treat population (ITT) consisted of all randomized patients that received at least one dose of study drug and had at least one postbaseline assessment of the primary or secondary efficacy variables. The per protocol (PP) population included patients in the ITT group who either discontinued the study because of an unsatisfactory response in the first 24 weeks or completed at least 22 weeks of treatment. Patients in the PP population must have had no major protocol violations during the first 24 weeks of the study, and a valid assessment of the primary efficacy variable no more than 7 days after receiving the last dose of study drug. The safety population consisted of all patients that received at least one dose of study drug and had at least one postbaseline safety assessment. Efficacy results at 24 weeks are based on PP population, whereas 52-week results are based on the ITT population.

Results

Patients

Table 1 summarizes the baseline demographic and metabolic characteristics of the patient cohort. A total of 576 patients were randomized. Groups appeared well balanced at baseline with a mean age, BMI, HbA_{1c} and FPG of approximately 57 years, 32 kg/m^2, 8.4% and 11.0 mmol/l respectively. Patients were predominantly Caucasian with a mean disease duration of 6.4 years. At baseline, the combined cohort had been using a mean metformin total daily dose of approximately 2000 mg daily for an average of 43 months; there were no significant differences in dose between the vildagliptin and the pioglitazone groups.

Primary Endpoint (24 Weeks)

When added to a stable dose of metformin (mean dose at baseline >2000 mg/day), both vildagliptin and pioglitazone

Table 1 Baseline demographics of the randomized population

Demographic variable	Vildagliptin 50 mg b.i.d. + metformin (N = 295)	Pioglitazone 30 mg q.d. + metformin (N = 281)
Age (years)		
Mean ± s.d.	56.3 ± 9.3	57.0 ± 9.7
Sex, n (%)		
Male	182 (61.7)	180 (64.1)
Female	113 (38.3)	101 (35.9)
Race, n (%)		
Caucasian	243 (82.4)	230 (81.9)
Hispanic or Latino	25 (8.5)	29 (10.3)
Black	9 (3.0)	7 (2.5)
Other	18 (6.1)	15 (5.3)
Body weight (kg)		
Mean ± s.d.	91.8 ± 18.5	91.2 ± 16.9
Body mass index (kg/m^2)		
Mean ± s.d.	32.2 ± 5.6	32.1 ± 5.1
Haemoglobin A_{1c} (%)		
Mean ± s.d.	8.4 ± 1.0	8.4 ± 0.9
Fasting plasma glucose (mmol/l)		
Mean ± s.d.	10.9 ± 2.6	11.0 ± 2.7
Disease duration (years)		
Mean ± s.d.	6.4 ± 4.9	6.4 ± 5.2
Metformin dose (mg)		
Mean ± s.d.	2032 ± 454	2008 ± 450

decreased HbA_{1c} (mean change from baseline: $-0.9 \pm 0.1\%$ and $1.0 \pm 0.1\%$ respectively) from identical baseline values ($8.4 \pm 0.1\%$) at 24 weeks. The between-group difference (PP population) in change in HbA_{1c} from baseline was 0.1% with CI: −0.05 to 0.26, establishing the non-inferiority of vildagliptin to pioglitazone as add-on therapy to metformin at the 0.3% non-inferiority margin [15].

Efficacy Over 52 Weeks

Figure 1 depicts the mean HbA_{1c} levels over the 52-week duration of the study in the ITT population. Vildagliptin appeared to show a faster onset of action than pioglitazone, with near maximal efficacy of vildagliptin seen by week 12 and of pioglitazone by week 24. Improvements in HbA_{1c} achieved in the first 12 weeks of the study were generally sustained with only a small increase between weeks 32 and 40, with this level maintained until the end of the study. At week 52, the mean change in HbA_{1c} from baseline in the vildagliptin group was −0.6% (CI: −0.71 to −0.45, $p < 0.001$) compared with −0.6% (CI: −0.77 to −0.52, $p < 0.001$) in the pioglitazone group. Patients with higher baseline HbA_{1c} generally had a greater reduction in HbA_{1c} in both treatment arms. A numerically greater reduction was noted in the vildagliptin arm in those with baseline $HbA_{1c} > 9\%$ where mean change in HbA_{1c} from baseline was $-1.1 \pm 0.2\%$ compared with $-0.9 \pm 0.2\%$ in the pioglitazone add-on group. Age more than 65 years did not impact greatly on the results, but there was some evidence of greater efficacy in non-obese patients (BMI < 30 kg/m^2) with vildagliptin than with pioglitazone, whereas the reverse occurred in obese patients (BMI≥ 30 kg/m^2), but none of these differences were tested statistically. Changes in HbA_{1c} from baseline in these patient subgroups are shown in table 2.

Both treatments resulted in significant reductions in mean FPG from baseline [vildagliptin:−1.0 mmol/l (CI: −1.30 to −0.66), $p < 0.001$ and pioglitazone: −1.6 mmol/l (CI: −1.95 to −1.33), $p < 0.001$] over 52 weeks. Of note, significant mean reductions from baseline also occurred at 24 weeks in both groups (vildagliptin: −1.4 mmol/l and pioglitazone: −2.1 mmol/l), although non-inferiority of vildagliptin to pioglitazone was not demonstrated at this point.

Body Weight

Over 52 weeks of treatment, body weight increased significantly in the pioglitazone group [2.6 (s.e. 0.3) kg, $p < 0.001$] but remained stable in the vildagliptin group [0.2 (s.e. 0.2) kg, non-significant change] (figure 2). The increase in weight associated with pioglitazone was more pronounced in patients with a baseline BMI ≥ 35 kg/m^2 where it was of the order of 3.9 kg compared with a decrease in weight of 0.1 kg with vildagliptin. This apparent difference was not because of different body weights at baseline (mean ± s.e. body weight at baseline in BMI≥ 35 kg/m^2 subgroup, vildagliptin vs. pioglitazone: 110.8 ± 1.7 vs. 109.2 vs. 1.7 kg).

Tolerability and Safety

Overall, AEs over 52 weeks occurred at similar frequencies with both vildagliptin (67.8%) and pioglitazone (68.2%). Most events were mild to moderate in severity.

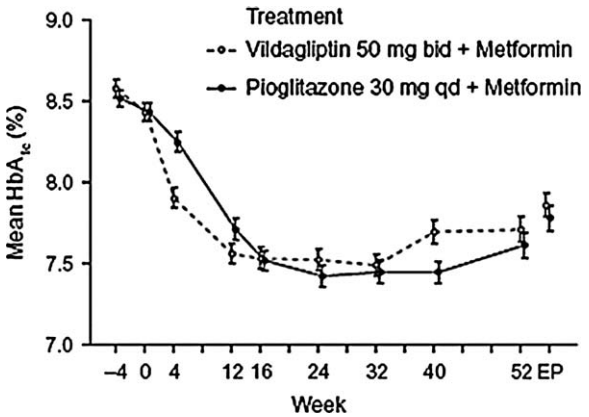

Fig. 1 Mean haemoglobin A_{1c} (HbA_{1c}) (± s.e.) during 52 weeks' treatment with vildagliptin 50 mg b.i.d. + metformin or pioglitazone 30 mg q.d. + metformin (intent-to-treat population). EP, endpoint.

Table 2 Subgroup analyses of mean change in HbA_{1c} from baseline to endpoint in the intent-to-treat population

	Mean ± s.e. change in HbA_{1c} (%) from baseline at week 52 [n (%)]	
Subgroup	**Vildagliptin 50 mg b.i.d. + metformin**	**Pioglitazone 30 mg q.d. + metformin**
Haemoglobin A_{1c} (%)		
≤8	−0.4 ± 0.1 [123 (42.0)]	−0.5 ± 0.1 [118 (42.6)]
All patients >8	−0.7 ± 0.1 [170 (58.0)]	−0.8 ± 0.1 [159 (57.4)]
All patients ≤9	−0.4 ± 0.1 [220 (75.1)]	−0.6 ± 0.1 [208 (75.1)]
>9	−1.1 ± 0.2 [73 (24.9)]	−0.9 ± 0.2 [69 (24.9)]
Body mass index (kg/m^2)		
<30	−0.8 ± 0.1 [117 (39.9)]	−0.4 ± 0.1 [107 (38.6)]
All patients ≥30	−0.4 ± 0.1 [175 (59.7)]	−0.8 ± 0.1 [170 (61.4)]
≥35	−0.4 ± 0.1 [81 (27.6)]	−0.7 ± 0.1 [75 (27.1)]
Age (years)		
<65	−0.6 ± 0.1 [239 (81.6)]	−0.6 ± 0.1 [207 (74.7)]
≥65	−0.6 ± 0.2 [54 (18.4)]	−0.7 ± 0.1 [70 (25.3)]

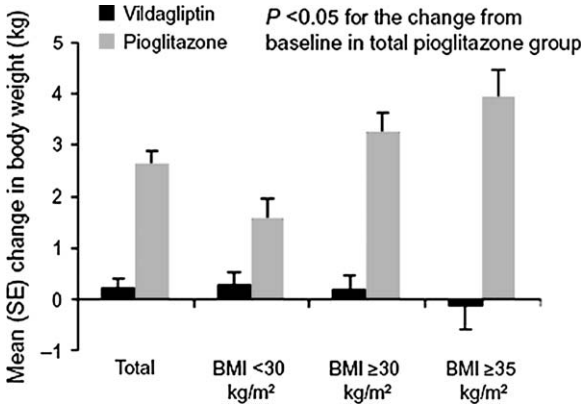

Fig. 2 Changes in body weight from baseline to endpoint. BMI, body mass index.

Headache, nasopharyngitis and peripheral oedema were the most commonly occurring AEs in both groups (table 3). The apparent increase in peripheral oedema seen in this study with vildagliptin, but not elsewhere in the vildagliptin database, has already been discussed in the previous report [15]. Hypoglycaemia occurred in one patient in both groups and was of grade 1 (mild) severity. There were no incidences of severe hypoglycaemia in either group.

The incidence of gastrointestinal AEs was numerically higher in the vildagliptin group compared with the pioglitazone group (20 vs. 14.6%); with vomiting (3.4 vs. 1.4%), nausea (3.4 vs. 1.8%), dyspepsia (2.7 vs. 1.1%) and constipation (3.4 vs. 1.4%) accounting for much of the difference. One patient in the vildagliptin group, with hepatic steatosis at baseline, experienced a hepatic-related AE (abnormal liver function test that led to withdrawal from the study) compared with four patients receiving pioglitazone (hepatic steatosis in two patients; hepatomegaly in one patient and abnormal liver function test in one patient). Skin-related AEs occurred in 1.7% of patients treated with vildagliptin and in 1.2% of pioglitazone-treated patients.

Table 3 Common occurring adverse events (≥5% in any group) during treatment in the safety population

Preferred term	Vildagliptin 50 mg b.i.d. + metformin (N = 295), n (%)	Pioglitazone 30 mg q.d. + metformin (N = 280), n (%)
Oedema, peripheral	32 (10.8)	31 (11.1)
Headache	19 (6.4)	17 (6.1)
Nasopharyngitis	16 (5.4)	20 (7.1)
Back pain	15 (5.1)	15 (5.4)
Dizziness	15 (5.1)	11 (3.9)
Diarrhoea	14 (4.7)	14 (5.0)

Serious AEs occurred more frequently in the pioglitazone group (8.9% of patients) than in the vildagliptin group (4.1%). The events underlying this apparent difference were varied, with no evidence of a trend in any event category. Clinically significant cardio- and cerebrovascular (CCV) events (confirmed by independent CCV adjudication committee) occurred in two (0.7%) vildagliptin-treated patients and six (2.1%) pioglitazone-treated patients. In the vildagliptin group, these events were acute coronary syndrome (one patient) and stroke (one patient). In the pioglitazone group, the events were acute coronary syndrome, arrhythmia, syncope and transient ischaemic attack (one patient each) and stroke (two patients). In the vildagliptin group, four patients experienced internal medicine (IM) AEs of clinical significance (confirmed by an independent IM adjudication committee) compared with none in the pioglitazone group. These were angio-oedema (one patient; treatment continued and the event resolved), gastrointestinal haemorrhage (two patients; treatment continued events resolved in both) and generalized urticaria (one patient; treatment was discontinued and event resolved). None of the events were suspected by the investigators of being related to study treatment.

Two patients in the vildagliptin group had a laboratory test of ALT or AST greater than three times but less than five times ULN, of whom one had a persistent elevation (elevated on more than one consecutive occasion or on consecutive measurements). In comparison, three patients in the pioglitazone group met these criteria, two of which had persistent elevations. Abnormal bilirubin levels were recorded in one patient treated with pioglitazone and in none of the patients treated with vildagliptin. There were no vildagliptin cases with ALT/AST $\geq 3\times$ ULN and bilirubin $\geq$ULN.

Discussion

Results from the initial period of this study have previously been reported in detail [15]. The results demonstrated that vildagliptin add-on treatment is non-inferior to pioglitazone in reduction in HbA_{1c} from baseline after 24 weeks. The main aim of continuing the study for a further 28 weeks was to assess the longer term tolerability and safety of vildagliptin. Nevertheless, the efficacy data reported at 52 weeks are important in demonstrating that both HbA_{1c} levels and change in HbA_{1c} from baseline were not noticeably different between the groups. There was an increase in HbA_{1c} between weeks 32 and 40 in the vildagliptin group, but HbA_{1c} levels were then maintained to week 52. Overall, durability of effect appears to be similar for vildagliptin and

pioglitazone when added to metformin, as HbA_{1c} levels at 52 weeks were similar. As with the 24-week data, there was evidence that pioglitazone had a greater effect on FPG, although both drugs resulted in a significant decrease in FPG from baseline.

Vildagliptin and pioglitazone were well tolerated as add-on therapy to metformin over 1 year with AEs occurring with similar frequencies in both treatment arms. Hypoglycaemia occurred rarely in both groups. Gastrointestinal events were more frequent with vildagliptin, but these were mostly mild to moderate in severity. Hepatic AEs and abnormal liver enzyme levels were uncommon in both groups. Of interest, in the report of the 24-week data, it was noted that peripheral oedema occurred more frequently in the vildagliptin group (8.8% of patients) than in the pioglitazone group (6.1% of patients) [15]. Whereas TZDs, including pioglitazone, are known to be associated with an increased risk of oedema [16–18], the frequency of this AE seemed abnormally high for vildagliptin. For example, only 2.2% of patients experienced peripheral oedema in a previous study of vildagliptin as an add-on to metformin [11]. Furthermore, as discussed by Bolli *et al.*, a pooled database involving 1855 patients receiving vildagliptin as monotherapy recorded peripheral oedema in 2.3% of patients [15]. Over 52 weeks, the proportion of patients experiencing peripheral oedema had risen to 10.8% in the vildagliptin group – an increase of 2% over an additional 28-week period. Thus, the proportion of patients who experienced peripheral oedema in the vildagliptin group in the second half of the study was as expected from earlier data. In comparison, the proportion of patients affected in the pioglitazone group had risen to 11.1% – an increase of 5% (similar to the proportion affected in the first 24 weeks). It appears there was an abnormally high occurrence of peripheral oedema in the vildagliptin group during the first 24 weeks of this study, which is not reflected in the second half of the study. One contributory factor, previously discussed by Bolli *et al.* [15], may have been concomitant use of amlodipine, an agent known to be associated with oedema. Six vildagliptin-treated patients who experienced peripheral oedema during the first 24 weeks were receiving amlodipine. None of the patients in the pioglitazone group who were receiving amlodipine experienced peripheral oedema.

There appeared to be a difference in the effect on body weight between the two treatment regimens in our study. In the earlier 24-week report, pioglitazone was associated with an increase in body weight of 1.9 kg [15]. Over the full 1-year duration, body weight continued to increase with pioglitazone, whereas the non-significant change in body weight in the vildagliptin group was maintained. Of note, the increase in body weight associated with pioglitazone seemed more pronounced in obese patients, particularly those with a BMI ≥ 35 kg/m^2, in whom a between-group difference of 4.0 kg occurred at study endpoint. However, this was not tested statistically.

In conclusion, vildagliptin 50 mg b.i.d., when added to patients with T2DM inadequately controlled on metformin, is well tolerated and results in numerically comparable decreases in HbA_{1c} levels to pioglitazone over 1 year. While pioglitazone added to metformin is associated with significant weight gain, vildagliptin is weight neutral and therefore represents a useful addition to pharmacotherapy in the management of type 2 diabetes.

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