Management of Type 2 Diabetes in Treatment-Naive Elderly Patients

Benefits and risks of vildagliptin monotherapy

Richard E. Pratley, MD[1]
Julio Rosenstock, MD[2]
F. Xavier Pi-Sunyer, MD[3]
Mary Ann Banerji, MD[4]
Anja Schweizer, PhD[5]
Andre Couturier, MSC[6]
Sylvie Dejager, MD, PhD[6]

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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From the [1]Vermont College of Medicine, Burlington, Vermont; the [2]Dallas Diabetes and Endocrine Center, Dallas, Texas; [3]St. Lukes-Roosevelt Hospital, New York, New York; [4]State University of New York Downstate Medical Center, Brooklyn, New York; [5]Novartis Pharma AG, Basel, Switzerland; and [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Address correspondence and reprint requests to Anja Schweizer, PhD, Novartis Pharma AG, Postfach, CH-4002 Basel, Switzerland. E-mail: anja.schweizer@novartis.com.

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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%)

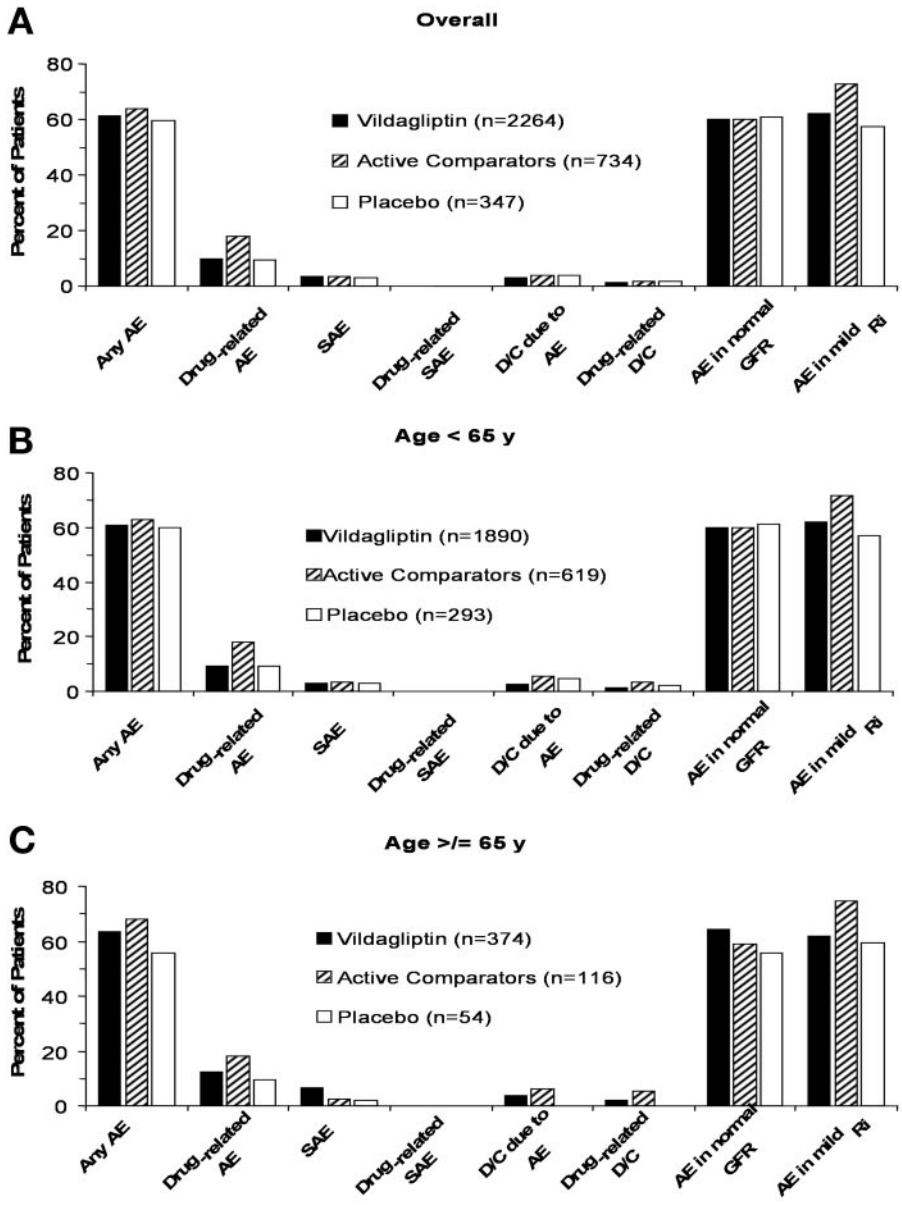

Figure 1— *Adverse events (AE) in patients receiving vildagliptin monotherapy, patients receiving monotherapy with any active comparator, and patients receiving placebo in the overall safety population* (A)*, the subgroup of patients aged <65 years* (B)*, and patients aged ≥65 years* (C)*. D/C, discontinued;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