Management of Type 2 Diabetes in Treatment-Naïve Elderly Patients: Benefits and Risks of Vildagliptin Monotherapy

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Running title: Vildagliptin in the elderly

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ABSTRACT

Objective: Evaluate the efficacy and safety of vildagliptin in elderly patients with type 2 diabetes.

Research Design and Methods: Efficacy data from 5 double-blind, randomized, placebo- or active-controlled trials of ≥24 week duration were pooled. Effects of 24-week vildagliptin monotherapy (100 mg daily) were compared in younger (<65 years, n=1231) and older (≥65 years, n=238) patients. Safety data from 8 controlled clinical trials of ≥12-week duration were pooled; AE profiles in younger (n=1890) and older (n=374) patients were compared.

Results: Mean baseline A1C and FPG were significantly lower in older (8.3±0.1% and 9.6±0.1 mmol/L, respectively; 70 years) than in younger (8.6±0.0% and 10.4±0.1 mmol/L; 50 years) 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 FPG was significantly larger in older (-1.5±0.2 mmol/L) than in younger patients (-1.1±0.1, P=0.035) patients. Body weight was significantly lower at baseline in older (83.4±1.0 kg) than in younger patients (92.0±0.6 kg) patients. Weight decreased significantly in the older subgroup (AMΔ= -0.9±0.3 kg, P=0.007), whereas smaller, non-significant decreases occurred in younger patients (AMΔ= -0.2±0.1 kg). AE rates were slightly higher in older than in younger subgroups, but lower among older, vildagliptin-treated subjects (63.6%) than in the pooled active comparator group (68.1%). Vildagliptin treatment did not increase AEs among older patients with mild renal impairment (62.0%). Hypoglycemia was rare (0.8%) in the elderly and no severe events occurred.

Conclusions: Vildagliptin monotherapy was effective and well tolerated in treatment-naïve elderly patients.

Abbreviations: ADA, American Diabetes Association; AE, Adverse Event; AMΔ, Adjusted Mean Change; DCCT, Diabetes Control and Complications Trial; DPP-4, Dipeptidyl Peptidase-IV; FDA, Food and Drug Administration; FPG, Fasting Plasma Glucose; GFR, Glomerular Filtration Rate; GIP, Glucose-dependent Insulinotropic Polypeptide; GLP-1, Glucagon-like Peptide-1; MDRD, Modification of Diet in Renal Disease (Study); MEDRA, Medical Dictionary for Regulatory Affairs; NGSP, National Glycohemoglobin Standardization Program; OAD, Oral Antidiabetic Drug; SAE, Serious Adverse Event; SMBG, Self-Monitored Blood Glucose; TG, Triglyceride; TZD, Thiazolidinedione

All Phase III trials described (NCT 00099905, NCT 00099866, NCT 00099918, NCT 00101673, NCT 00101803, NCT 00120536) are registered with ClinicalTrials.gov.
Type 2 diabetes is among the most common chronic conditions in older adults. Nearly 20% of individuals aged ≥65 years are afflicted, although nearly half of them are undiagnosed (1). Management of type 2 diabetes in the elderly can be particularly challenging for a number of reasons (2). Firstly, hypoglycemia is more common in older than in younger people taking oral antidiabetic drugs (OADs), often more severe, and can precipitate serious events such as falls and hip fractures. This 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. Secondly, 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 more than 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-naïve patients with type 2 diabetes, 24-week treatment with vildagliptin monotherapy (50 or 100 mg daily) was reported to decrease A1C by 0.9% to 1.1% (7,8).

Because the effects of incretin hormones to increase insulin secretion (9) and of 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 the elderly.

The purpose of the present analysis is 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 was compared to that in patients <65 years of age.

**RESEARCH DESIGN AND METHODS**

**Study designs.** Studies were multicenter, randomized, double-blind, parallel-group, placebo- or active-controlled trials of 12 to 52 weeks’ duration, with one or more vildagliptin monotherapy arms. Twenty-four-week efficacy data from all completed trials of ≥24 week duration were pooled, (patients receiving vildagliptin 100 mg daily as monotherapy, either 50 mg bid or 100 mg qd) from 2 placebo-controlled and 3 active-controlled studies (n=1469). To provide the most comprehensive information available, safety data from all completed trials of ≥12 weeks’ duration (ie, the aforementioned 5 trials, 2 placebo-controlled, 12-week studies and one active-controlled, 12-week study) were pooled from patients receiving vildagliptin 50 mg qd, 50 mg bid, or 100 mg qd (n=2264), all active comparators (metformin up to 1000
mg bid, pioglitazone 30 mg qd, or
rosiglitazone 8 mg qd, n=735), and placebo
(n=347).

Details regarding study designs and
inclusion and exclusion criteria are
summarized in the online appendix (Table
A1) and provided in the individual study
publications (7,8,11-13).

Study assessments. A1C, FPG, body
weight, fasting lipid levels (triglycerides
[TG], 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 pre-specified subgroups of
patients with lower (≤8.0% or ≤9.0%) and
higher baseline A1C levels (>8.0% or
>9.0%) and of patients with lower (<30
kg/m² or <35 kg/m²) and higher (≥30 kg/m²
or ≥35 kg/m²) baseline BMI. Changes in
body weight were assessed in the same BMI
subgroups. In addition, responder analyses
were performed, determining the percentage
of patients achieving A1C <7.0% in the
overall population and in the pre-specified
subgroups of patients with a baseline A1C
≤8%.

Glomerular filtration rate (GFR) was
estimated with the MDRD method (14), and
patients were classified according to criteria
previously specified in guidances published
by the FDA into a group with normal renal
function (>80 mL/min x 1.73/m²) and a
group with mild renal impairment (GFR
≤80 and >50 mL/min x 1.73/m²). All
adverse events (AEs) were recorded and
assessed by the investigator as to the
severity and possible relationship to 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 SMBG
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; Bioanalytical
Research Corporation (BARC) BARC-US
(Lake Success, NY), BARC-EU (Ghent,
Belgium), Diabetes Diagnostics Laboratory
(Columbia, MO), Covance-US
(Indianapolis, IN), or Medical Research
Laboratories International (Zaventem,
Belgium). A1C was measured by HPLC
(ion exchange or boronate affinity). All
laboratories were either National
Glycohemoglobin Standardization Program
(NGSP) certified or NGSP network
laboratories, thus allowing traceability to
the DCCT 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 post-baseline
safety assessment was available. The
Efficacy Population comprised all patients
receiving vildagliptin (100 mg daily; 50 mg
bid or 100 mg qd) for whom both a baseline
and post-baseline efficacy assessment were
available. Changes from baseline in efficacy
parameters were analyzed using an
ANCOVA model containing treatment,
study, age group, treatment by age group
interaction, and baseline value as a
covariate. Within-group comparisons
(endpoint vs baseline) and between-group
comparisons (patients aged ≥65 years vs
<65 years) were made using 2-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
RESULTS

Patients studied. 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 approximately 17% of the pooled safety database. The majority of all patients were Caucasian and obese (with only about half the prevalence of severe obesity than in the younger subgroup), with a mean A1C of 8.6% and mean FPG of 10.1 mmol/L. Minorities represented a larger proportion of the younger subgroup, while the older subgroup was on average less obese 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 2/3 of the older patients had undiagnosed mild renal impairment (vs ~28% of the younger subgroup). More than 75% of the older subgroup had been diagnosed with hypertension, about half with dyslipidemia, and nearly 25% with coronary artery disease, while 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 enrollment compared to 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 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 \(\text{AM}\Delta = -1.2\%\)) tended to be greater (\(P=0.092\)) than that in the younger subgroup (AM\(\Delta = -1.0\%\)) despite having a significantly lower baseline A1C (8.3% vs 8.7%). Since 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 an AM\(\Delta\) 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).

In the case of 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 (AM\(\Delta\) = -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 ADA-recommended target A1C (<7.0%) versus 36% of the younger subgroup (\(P=0.002\) for younger vs. older). In patients with baseline A1C ≤8.0% (mean of 7.6% in both subgroups), the percentage of patients achieving target was also significantly greater for the elderly (63%) than for the younger patients (52%, \(P=0.034\) younger vs older).

Vildagliptin did not significantly affect body weight relative to baseline in the overall population (AM\(\Delta\) = -0.3 kg) or in the younger subgroup (AM\(\Delta\) = -0.2 kg). In contrast, in older patients, vildagliptin significantly decreased body weight (AM\(\Delta\) = -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. 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 to younger patients, across all pre-specified subgroups (Table 1). Although reductions in A1C were somewhat larger in the leaner subgroups, the enhanced efficacy of vildagliptin in older vs 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 AE profiles in the overall Safety Population (Panel A) and in the younger (Panel B) and older (Panel C) subgroups. AEs were slightly more frequent in older (63.6%) than younger patients receiving vildagliptin (60.6%), but a more substantial difference was seen for the pooled active comparator group (68.1% in the elderly vs 63.0% in the younger subgroup). Further, no excess of AEs in elderly vs younger patients with mild renal impairment receiving vildagliptin (62.0% vs 62.1%) and no excess in older patients with mild renal impairment compared to older patients with normal renal function (62.0% vs 63.6%) were noted, while the AE rate in renally-impaired patients receiving an active comparator was higher for both older (74.6%) and younger (71.7%) patients. AEs 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 AEs 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” (MEDRA 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 possibly 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 AE were slightly more frequent in older (3.7%) than 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 AEs occurring in elderly patients and the incidence of those specific AEs in the overall Safety Population and in the younger subgroup is provided in the online appendix (Table A3). The frequency of any specific AE 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%, 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 2264 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 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 post-operative bleeding and septic shock following surgery for a small bowel obstruction. Two patients receiving an active comparator died, both of which 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.

While 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 co-medications make the management of type 2 diabetes considerably more difficult in the elderly. Despite these potential problems, the overall AE 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 AEs in older compared to younger patients receiving vildagliptin. Additionally, in older patients, the incidence of AEs in patients with mild renal impairment was similar to that in patients with normal renal function with vildagliptin treatment. In contrast, the AE rate in younger and older patients with mild renal impairment receiving an active comparator was higher than in patients with normal renal function. Since 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 that the incidence of hypoglycemia was very low (0.8%) in elderly patients receiving vildagliptin, and 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-week treatment with vildagliptin (100 mg daily) vs 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 AE, drug-related AEs, and
AEs 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 AEs, such as peripheral edema, nausea or diarrhea, were less frequently reported with vildagliptin vs. active comparators (metformin and TZDs).

A relatively benign AE profile is an important consideration for treatment of type 2 diabetes in older patients in whom metformin should be used with caution in case of altered renal function, sulfonylureas present a well documented risk of hypoglycemia, and TZDs 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 the safety of vildagliptin in elderly patients.

The influence of vildagliptin monotherapy on all efficacy parameters in drug-naïve 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 mM) than in the younger (Δ= -1.1 mM) 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 ADA-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 non-diabetic 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 the 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). Since 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, since the GIP response to nutrient intake is exaggerated in elderly patients with type 2 diabetes (16), this may compensate for the impaired β-cell responsiveness to GIP seen in the elderly (19) and in patients with type 2 diabetes (20).

The mechanism by which vildagliptin treatment leads to modest weight loss in the elderly is unclear, but is not attributable to gastrointestinal upset, since gastrointestinal AEs were reported by few patients, and somewhat less frequently in the elderly than in the younger subgroup (eg, nausea incidence of 1.9% vs 2.7%, respectively). Moreover, subgroup analyses
established that more weight loss was generally seen in more obese subjects, while the elderly 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-naïve 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.

ACKNOWLEDGMENTS

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REFERENCES


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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n = 1469)</th>
<th>Aged &lt;65 y (n = 1231)</th>
<th>Aged ≥65 y (n = 238)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>AMΔ</td>
<td>Baseline</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.6 ± 0.0</td>
<td>-1.0 ± 0.0&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8.7 ± 0.0</td>
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<tr>
<td>FPG (mmol/L)</td>
<td>10.4 ± 0.1</td>
<td>-1.1 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>10.5 ± 0.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>90.6 ± 0.5</td>
<td>-0.3 ± 0.1</td>
<td>92.0 ± 0.6</td>
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Responder Analyses (achieving A1C <7.0%)

<table>
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<tr>
<th>Parameter</th>
<th>Overall</th>
<th>Baseline A1C ≤8.0%</th>
<th>Baseline A1C &gt;8.0%</th>
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<tr>
<td></td>
<td>n*</td>
<td>n (%)</td>
<td>n*</td>
</tr>
<tr>
<td>Fasting lipids (mmol/L)</td>
<td>AM%Δ</td>
<td>AM%Δ</td>
<td>AM%Δ</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.4 ± 0.1</td>
<td>-3.3 ± 1.3&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>2.4 ± 0.1</td>
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<tr>
<td>Total cholesterol</td>
<td>5.3 ± 0.0</td>
<td>-2.2 ± 0.4&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>5.3 ± 0.0</td>
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<tr>
<td>LDL</td>
<td>3.1 ± 0.0</td>
<td>-0.7 ± 0.8</td>
<td>3.1 ± 0.0</td>
</tr>
<tr>
<td>HDL</td>
<td>1.2 ± 0.0</td>
<td>4.5 ± 0.6&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1.1 ± 0.0</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>4.1 ± 0.0</td>
<td>-3.3 ± 0.6&lt;sup&gt;‡&lt;/sup&gt;</td>
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<tr>
<td>VLDL</td>
<td>0.95 ± 0.01</td>
<td>-3.4 ± 1.1&lt;sup&gt;‡&lt;/sup&gt;</td>
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Blood pressure (mm Hg)

<table>
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<tr>
<th>Parameter</th>
<th>Diastolic</th>
<th>Systolic</th>
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<tbody>
<tr>
<td></td>
<td>mean Δ</td>
<td>mean Δ</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81.3 ± 0.3</td>
<td>-1.4 ± 0.2&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic</td>
<td>132.1 ± 0.3</td>
<td>-2.2 ± 0.3&lt;sup&gt;‡&lt;/sup&gt;</td>
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Subgroup Analyses

A1C (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BL (n)</th>
<th>AMΔ</th>
<th>BL (n)</th>
<th>AMΔ</th>
<th>BL (n)</th>
<th>AMΔ</th>
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<tbody>
<tr>
<td>BL A1C ≤8.0%</td>
<td>8.7 (613)</td>
<td>-1.2 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>8.8 (487)</td>
<td>-1.2 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>8.4 (126)</td>
<td>-1.3 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>BL A1C &gt;8.0%</td>
<td>8.1 (995)</td>
<td>-0.8 ± 0.0&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>8.1 (806)</td>
<td>-0.7 ± 0.0&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>7.9 (189)</td>
<td>-0.9 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>BL A1C &gt;9.0%</td>
<td>9.9 (474)</td>
<td>-1.6 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>9.9 (425)</td>
<td>-1.6 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>9.7 (49)</td>
<td>-1.7 ± 0.2&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>BL BMI &lt;30 kg/m²</td>
<td>8.6 (400)</td>
<td>-0.9 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>8.6 (302)</td>
<td>-0.9 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>8.5 (98)</td>
<td>-1.0 ± 0.1&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI Category</td>
<td>Baseline Body Weight (kg)</td>
<td>Δ Weight Change (kg)</td>
<td>Value at Endpoint (kg)</td>
<td>P Value</td>
<td>Δ Weight Change (kg)</td>
<td>Value at Endpoint (kg)</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>BL BMI ≥30 kg/m²</td>
<td>8.6 (855)</td>
<td>-0.9 ± 0.1 †</td>
<td>8.7 (743)</td>
<td>-0.9 ± 0.1 †</td>
<td>8.2 (112)</td>
<td>-1.0 ± 0.1 †</td>
</tr>
<tr>
<td>BL BMI &lt;35 kg/m²</td>
<td>8.7 (1034)</td>
<td>-1.1 ± 0.0 †</td>
<td>8.8 (838)</td>
<td>-1.1 ± 0.0 †</td>
<td>8.3 (196)</td>
<td>-1.2 ± 0.1 †</td>
</tr>
<tr>
<td>BL BMI ≥35 kg/m²</td>
<td>8.6 (434)</td>
<td>-0.9 ± 0.1 †</td>
<td>8.6 (392)</td>
<td>-0.9 ± 0.1 †</td>
<td>8.2 (42)</td>
<td>-0.9 ± 0.2 †</td>
</tr>
<tr>
<td><strong>Body Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL BMI &lt;30 kg/m²</td>
<td>75.6 (613)</td>
<td>-0.0 ± 0.1</td>
<td>75.8 (487)</td>
<td>0.1 ± 0.1</td>
<td>74.5 (126)</td>
<td>-0.5 ± 0.3 †</td>
</tr>
<tr>
<td>BL BMI ≥30 kg/m²</td>
<td>101.3 (855)</td>
<td>-0.6 ± 0.2 †</td>
<td>102.6 (743)</td>
<td>-0.5 ± 0.2 †</td>
<td>93.3 (112)</td>
<td>-1.3 ± 0.4 †‡</td>
</tr>
<tr>
<td>BL BMI &lt;35 kg/m²</td>
<td>82.1 (1034)</td>
<td>-0.2 ± 0.1</td>
<td>82.8 (838)</td>
<td>-0.1 ± 0.1</td>
<td>79.4 (196)</td>
<td>-0.8 ± 0.2 †‡</td>
</tr>
<tr>
<td>BL BMI ≥35 kg/m²</td>
<td>110.7 (434)</td>
<td>-0.6 ± 0.3 †</td>
<td>111.7 (392)</td>
<td>-0.6 ± 0.3 †</td>
<td>101.8 (42)</td>
<td>-1.4 ± 0.7 †‡</td>
</tr>
</tbody>
</table>

*Patients with both baseline A1C ≥7% and an endpoint value; †P<0.05 vs younger subgroup; ‡P<0.05 vs baseline (within group)
Figure 1: Adverse events (AE) in patients receiving vilagliptin monotherapy (closed bars), patients receiving monotherapy with any active comparator (hashed bars) and patients receiving placebo (open bar) in the overall Safety Population (Panel A), the subgroup of patients aged <65 years (Panel B) and patients aged ≥65 years (Panel B). D/C = discontinued; GFR = glomerular filtration rate; RI = renal impairment.