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Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy

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Aim: To examine the efficacy and safety of vildagliptin vs. glimepiride as add-on therapy to metformin in patients with type 2 diabetes mellitus in a 52-week interim analysis of a large, randomized, double-blind, multicentre study. The primary objective was to demonstrate non-inferiority of vildagliptin vs. glimepiride in glycosylated haemoglobin (HbA_{1c}) reduction at week 52.
Methods: Patients inadequately controlled on metformin monotherapy (HbA_{1c} 6.5–8.5%) and receiving a stable dose of metformin (mean dose 1898 mg/day; mean duration of use 36 months) were randomized 1:1 to receive vildagliptin (50 mg twice daily, n = 1396) or glimepiride (titrated up to 6 mg/day; mean dose 4.5 mg/day, n = 1393).
Results: Non-inferiority of vildagliptin was demonstrated (97.5% confidence interval 0.02%, 0.16%) with a mean (SE) change from baseline HbA_{1c} (7.3% in both groups) to week 52 endpoint of −0.44% (0.02%) with vildagliptin and −0.53% (0.02%) with glimepiride. Although a similar proportion of patients reached a target HbA_{1c} level of <7% with vildagliptin and glimepiride (54.1 and 55.5%, respectively), a greater proportion of patients reached this target without hypoglycaemia in the vildagliptin group (50.9 vs. 44.3%; $p < 0.01$). Fasting plasma glucose (FPG) reductions were comparable between groups (mean [SE] −1.01 [0.06] mmol/l and −1.14 [0.06] mmol/l respectively). Vildagliptin significantly reduced body weight relative to glimepiride (mean [SE] change from baseline −0.23 [0.11] kg; between-group difference −1.79 kg; $p < 0.001$) and resulted in a 10-fold lower incidence of hypoglycaemia than glimepiride (1.7 vs. 16.2% of patients presenting at least one hypoglycaemic event; 39 vs. 554 hypoglycaemic events, $p < 0.01$). No severe hypoglycaemia occurred with vildagliptin compared with 10 episodes with glimepiride ($p < 0.01$), and no patient in the vildagliptin group discontinued because of hypoglycaemia compared with 11 patients in the glimepiride group. The incidence of adverse events (AEs), serious AEs and adjudicated cardiovascular events was 74.5, 7.1 and 0.9%, respectively, in patients receiving vildagliptin, and 81.1, 9.5 and 1.6%, respectively, in patients receiving glimepiride.
Conclusions: When metformin alone fails to maintain sufficient glycaemic control, the addition of vildagliptin provides comparable efficacy to that of glimepiride after 52 weeks and displays a favourable AE profile, with no weight gain and a significant reduction in hypoglycaemia compared with glimepiride.

Keywords: DPP-4 inhibitor, glimepiride, hypoglycaemia, type 2 diabetes mellitus, vildagliptin
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Duality of interests:
E. F. has received consulting fees from Novartis Pharmaceuticals. V. F. has received funding for research and consulting/speaking for Novartis as well as from other manufacturers of drugs in this class, including Merck, NovoNordisk, Eli Lilly, Takeda and Glaxo. B. Z. has received research support and consulting fees from Novartis Pharmaceuticals. B. A. has received funding and consulting fees from Novartis Pharmaceuticals. D. M. has received consulting fees from Novartis as well as from other manufacturers of drugs in this class, including NovoNordisk and MSD. He has also received lecturing honoraria from Eli Lilly and NovoNordisk. S. B., Q. S. and S. D. are employees of Novartis Pharmaceuticals.
This trial (NCT00106340) is registered with ClinicalTrials.gov.

Introduction

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that prevents the rapid degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and increases plasma levels of their intact, active form [1–5]. Vildagliptin also improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) either as monotherapy [6–9] or in combination with metformin [10,11], a thiazolidinedione (TZD) [12,13], a sulfonylurea (SU) [14] or insulin [15]. This improvement in glycaemic control is mediated primarily by an enhancement of pancreatic islet function, with improved β- and α-cell sensitivity to glucose [16]. In addition, vildagliptin is weight neutral and is associated with minimal risk of hypoglycaemia either as monotherapy or in combination with metformin, SU, TZD or insulin [17]. When added to insulin, vildagliptin significantly lowers the incidence and severity of hypoglycaemic episodes compared with placebo [15]. This low hypoglycaemic risk probably relates to the fact that GLP-1 enhancement of insulin secretion and inhibition of glucagon secretion are glucose dependent [18]. This is further evidenced in patients recently diagnosed with mild hyperglycaemia [baseline glycosylated haemoglobin (HbA_{1c}) 6.7% and FPG 7.1 mmol/l], where vildagliptin treatment resulted in no hypoglycaemic episodes over 1 year [19].

To evaluate the positioning of DPP-4 inhibitors as add-on to metformin when metformin alone is not sufficient to achieve glycaemic control, the long-term efficacy and safety of vildagliptin vs. SU was examined in a multicentre, randomized, double-blind, active-controlled study. The study compared vildagliptin (50 mg twice daily) with glimepiride (up to 6 mg/day) in patients with T2DM inadequately controlled with metformin monotherapy. In this study, we report findings from a preplanned 52-week interim analysis.

Methods

Inclusion and Exclusion Criteria

Patients attended one screening visit (week -4, visit 1) where inclusion and exclusion criteria were assessed. Male and female patients (non-fertile or using a medically approved birth control method) with T2DM and HbA_{1c} of 6.5–8.5%, who had received metformin for ≥3 months and were on a stable dose of ≥1500 mg daily for a minimum of ≥4 weeks prior to visit 1, were aged 18–73 years and had a body mass index (BMI) of 22–45 kg/m^2 were eligible to participate.

Patients with a history of type 1 diabetes or secondary forms of diabetes were excluded, as were those who had experienced acute metabolic diabetic complications in the past 6 months, acute infections that might affect blood glucose control in the 4 weeks prior to visit 1, serious cardiac conditions (history of torsades de pointes or ventricular tachycardia; percutaneous coronary intervention in the past 3 months; myocardial infarction, coronary artery bypass surgery, unstable angina or stroke in the past 6 months; congestive heart failure requiring pharmacological treatment; second- or third-degree atrioventricular block or prolonged QTc) or clinically significant liver or renal disease. Any of the following laboratory abnormalities at screening also precluded participation: alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN), direct bilirubin >1.3 times ULN, serum creatinine levels ≥132 μmol/l in men or ≥123 μmol/l in women, clinically significant thyroid-stimulating hormone outside of normal range at screening; or fasting triglycerides >7.9 mmol/l.

Study Design

This was a multicentre, randomized, double-blind, active-controlled study. Eligible patients were randomized 1:1 at baseline (day 0) to receive vildagliptin (50 mg twice daily) or glimepiride (starting dose 2 mg/day) in addition to metformin (dose remained unchanged). Further visits were scheduled at weeks 4, 8, 12, 16, 20, 24, 32, 40, 46 and 52. Glimepiride/matched control could be up-titrated (to a maximum of 6 mg/day) at weeks 4, 8 or any later visit if FPG exceeded 6.2 mmol/l or down-titrated in cases of recurrent hypoglycaemia. After week 24, rescue medication (pioglitazone) could be prescribed if patients reached the highest tolerated glimepiride dose/matched control and whose HbA_{1c} was >8.0%. Approximately 6000 patients were screened to randomize 3000 patients; the interim analysis was carried out once ~2800 patients had completed (or would have completed) 52 weeks of treatment.

Efficacy and Safety Assessments

The primary efficacy assessment was change in HbA_{1c} from baseline. All HbA_{1c} measurements were performed by a central laboratory. Secondary efficacy assessments included HbA_{1c} responder rates and HbA_{1c} reduction by baseline HbA_{1c} category, age group, FPG and body weight. All adverse events (AEs), serious AEs and their severity and relationship to study drug were monitored. Hypoglycaemic events (defined as symptoms suggestive of hypoglycaemia and confirmed by self-monitored

plasma glucose <3.1 mmol/l) and severe hypoglycaemia (any episode requiring the assistance of another party) were also recorded.

Statistical Analyses

The primary objective of the interim analysis was to demonstrate non-inferiority of vildagliptin 50 mg twice daily vs. glimepiride in reducing HbA_{1c} levels from baseline to week 52 (non-inferiority margin: upper limit of the 97.5% confidence interval [CI] <0.3%; endpoint: last available post-randomization assessment before rescue medication initiation, up to and including week 52 using the last observation carried forward). The primary analysis was based on the per protocol (PP) population. Primary and secondary endpoint changes from baseline were assessed using an analysis of covariance model (ANCOVA; classification variables: treatment and pooled centre; covariate: baseline value).

Patient Populations

The randomized (RAN) population was the first 2800 randomized patients who completed (or who would have completed) 52 weeks in the study, with completely cleaned and locked efficacy and safety data. There were 2789 randomized patients included in this interim analysis. The safety (SAF) population comprised patients who received at least one dose of study drug and had at least one post-baseline safety assessment, up to and including the week 52 visit. The PP population included patients in any of the following categories: (i) completed at least 48 weeks of treatment without taking rescue medication and without major protocol violation; (ii) began rescue medication owing to lack of efficacy after 24 weeks of treatment (as per protocol) without major protocol violation; and (iii) discontinued the study owing to lack of efficacy (as per protocol) without major protocol violation. The intent-to-treat (ITT) population was made up of patients included in the RAN population who received at least one dose of study drug and had at least one post-baseline assessment of the primary efficacy variable HbA_{1c}.

Cardiovascular and Cerebrovascular Adjudication Committee

An independent cardiovascular and cerebrovascular (CCV) adjudication committee reviewed all occurrences of CCV events in a blinded fashion. In addition, the committee reviewed all occurrences of prespecified electrocardiogram (ECG) changes, which were reported either as a new finding at the end-of-study/post-baseline ECG or as an AE.

Ethics

The study was conducted according to the ethical principles of the Declaration of Helsinki. The study and any amendments were reviewed by the independent ethics committee or institutional review board for each centre. Written, informed consent was obtained from each subject before randomization.

Results

Patient Disposition

From a total of 2789 randomized patients (vildagliptin 1396 and glimepiride 1393), 1174 (84.1%) and 1118 (80.3%) completed 52 weeks of treatment respectively. The most common reasons for discontinuation were consent withdrawal (5.9 and 7.3%, respectively; not significant) and AEs (4.8 and 7.7%, respectively; $p < 0.01$). The excess dropouts from the glimepiride group were driven by hypoglycaemia-related AEs, such as tremor (0.9%) and hypoglycaemia (0.8%). Discontinuation because of lack of therapeutic effect, however, was similar with vildagliptin and glimepiride (1.2 and 1.1% respectively). Of the patients who completed the 52-week study period, 1118 (vildagliptin) and 1072 (glimepiride) patients were included in the PP analysis (see figure 1 for patient disposition).

Patient Demographics and Baseline Characteristics

Patient demographics were well balanced between groups (table 1). Patients in the randomized population were predominantly Caucasian (85.8%) and male (53.4%), with a mean age of 57.5 years and BMI of 31.8 kg/m^2. Baseline HbA_{1c} and FPG were comparable between groups (vildagliptin: mean 7.31% and 9.16 mmol/l, respectively; glimepiride: mean 7.30% and 9.16 mmol/l, respectively). Duration of T2DM (mean 5.7 and 5.8 years, respectively) and duration of metformin use (35.8 and 36.0 months, respectively) were also similar between the vildagliptin and the glimepiride treatment groups. At randomization, mean metformin dose was 1904 and 1893 mg/day, respectively, in the vildagliptin and glimepiride groups. During the study, mean glimepiride dose was ~4.1 mg/day at week 12, increasing to 4.5 mg/day by week 52.

Overall, cardiovascular (CV) risk factors were well balanced between groups. In both treatment groups, over half

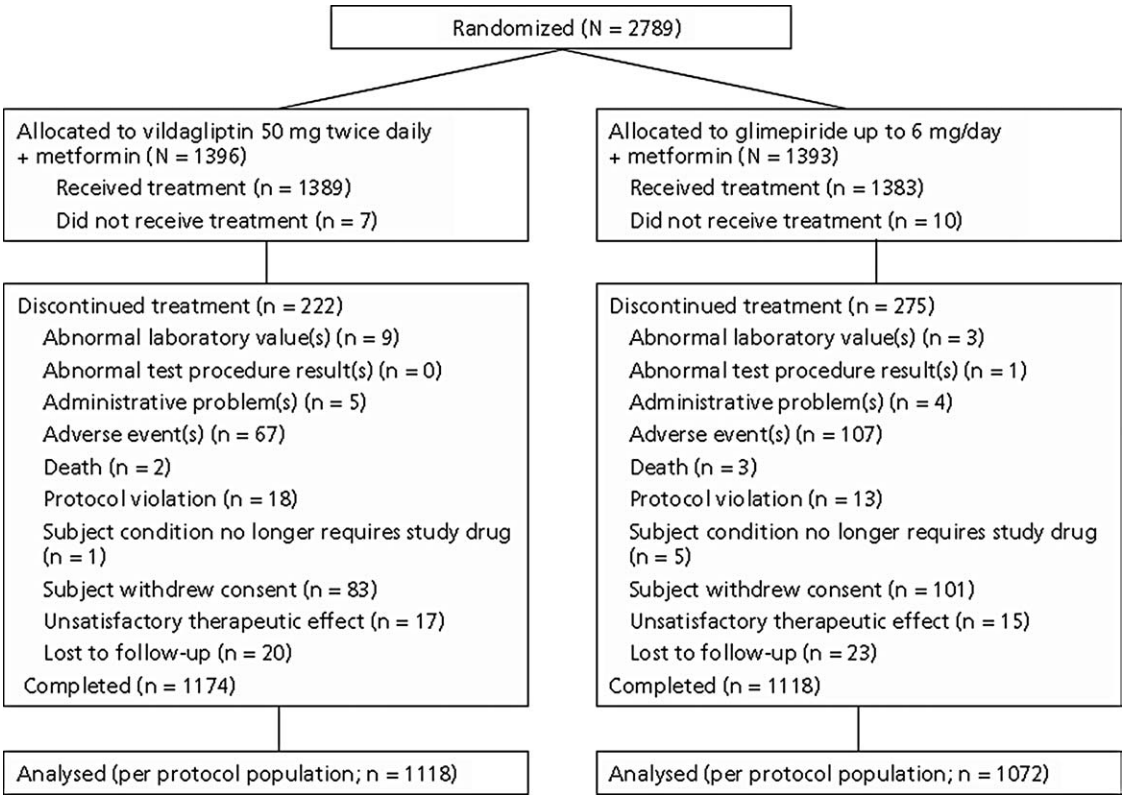

Fig. 1 Patient disposition (randomized population).

of the patients were classified as obese, with more than a quarter being morbidly obese (BMI $\geq$35 kg/m^2) and approximately a third of men and 40% of women having abdominal obesity [waist circumference >102 cm (men) or >88 cm (women)]. Approximately a sixth of patients were smokers. There was little difference between the number of patients who had hypertension (64.6% in the vildagliptin group and 68.5% in the glimepiride group), dyslipidaemia (49.3 and 50.0%) or mild [glomerular filtration rate (GFR) estimated using the MDRD formula: 60–90 ml/min/1.73 m^2] or moderate (GFR: 30–60 ml/min/1.73 m^2) renal insufficiency (44.7 and 4.7% of vildagliptin patients; 43.1 and 5.0% of glimepiride patients). The overall incidence of previous cardiac disorders was also well balanced between the vildagliptin and the glimepiride treatment groups (19.2 and 19.6%, respectively).

Concomitant Medications

The majority of patients received concomitant therapies during the study, in similar proportions in each group (vildagliptin group, 93.1%; glimepiride group, 93.9%). The most common were antihypertensive agents (the majority of which were angiotensin-converting enzyme inhibitors, administered in approximately 43% of all patients and angiotensin II receptor antagonists and β-blockers in 22–24% of patients either alone or in combination with diuretics), lipid-lowering agents [in ~47% of patients, mostly statins (about 42% of patients) in both groups] and platelet aggregation inhibitors (in a third of patients).

Efficacy

At week 52, adjusted mean (SE) change in HbA_{1c} from baseline was −0.44% (0.02%) with vildagliptin and −0.53% (0.02%) with glimepiride (figures 2 and 3), establishing non-inferiority of vildagliptin as the upper 97.5% CI limit for the between-group difference (0.02%, 0.16%) did not exceed the prespecified 0.3% margin in the PP population. Comparable results were seen for the ITT population. With vildagliptin, mean HbA_{1c} decreased to 6.81% by weeks 12–16 and remained essentially stable thereafter with a mean HbA_{1c} of 6.75% at week 52 (figure 2). With glimepiride, the greatest reduction was reached at week 16 (mean: 6.60%) with a mean HbA_{1c} of 6.71% by week 52. Use of rescue

Table 1 Patient demographics and baseline characteristics (randomized population)

Demographic	Vildagliptin (50 mg twice daily) n = 1396	Glimepiride (up to 6 mg/day) n = 1393	Total n = 2789
Age (years), mean ± SD	57.50 ± 9.06	57.46 ± 9.28	57.48 ± 9.17
Age group			
< 65 years	1045 (74.9%)	1032 (74.1%)	2077 (74.5%)
≥ 65 years	351 (25.1%)	361 (25.9%)	712 (25.5%)
Sex			
Male	737 (52.8%)	753 (54.1%)	1490 (53.4%)
Female	659 (47.2%)	640 (45.9%)	1299 (46.6%)
Race			
Caucasian	1205 (86.3%)	1187 (85.2%)	2392 (85.8%)
Black	18 (1.3%)	19 (1.4%)	37 (1.3%)
Asian	44 (3.2%)	44 (3.2%)	88 (3.2%)
Hispanic or Latino	124 (8.9%)	129 (9.3%)	253 (9.1%)
Others	5 (0.4%)	14 (1.0%)	19 (0.7%)
BMI (kg/m^2), mean ± SD	31.80 ± 5.27	31.69 ± 5.25	31.75 ± 5.26
HbA_{1c} (%), mean ± SD	7.31 ± 0.64	7.30 ± 0.65	7.30 ± 0.65
FPG (mmol/l), mean ± SD	9.16 ± 2.29	9.16 ± 2.23	9.16 ± 2.26
Duration of type 2 diabetes mellitus (years), mean ± SD	5.71 ± 5.18	5.75 ± 5.03	5.73 ± 5.11
Duration of metformin use at randomization (months), mean ± SD	35.83 ± 34.66	36.04 ± 35.35	35.93 ± 35.00
Total daily metformin dose at randomization (mg), mean ± SD	1903.90 ± 413.47	1892.64 ± 408.00	1898.28 ± 410.71
Cardiovascular risk factors			
Obese (BMI ≥30 kg/m^2)	822 (58.9%)	798 (57.3%)	1620 (58.1%)
Morbidly obese (BMI ≥35 kg/m^2)	381 (27.3%)	352 (25.3%)	733 (26.3%)
Men with abdominal obesity >102 cm	447 (32.0%)	434 (31.2%)	881 (31.6%)
Women with abdominal obesity >88 cm	561 (40.2%)	535 (38.4%)	1096 (39.3%)
Smokers	235 (16.8%)	219 (15.7%)	454 (16.3%)
Mild renal insufficiency (GFR: 60–90 ml/min/1.73 m^2)	624 (44.7%)	600 (43.1%)	1224 (43.9%)
Moderate renal insufficiency (GFR: 30–60 ml/min/1.73 m^2)	65 (4.7%)	69 (5.0%)	134 (4.8%)
Hypertension	902 (64.6%)	954 (68.5%)	1856 (66.5%)
Dyslipidaemia	688 (49.3%)	696 (50.0%)	1384 (49.6%)
Previous cardiac disorder	268 (19.2%)	273 (19.6%)	541 (19.4%)

BMI, body mass index; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin.

medication was minimal with both vildagliptin and glimepiride (5.1 and 3.7% of treated patients respectively).

Greater mean HbA_{1c} reductions from baseline to week 52 were seen in the predefined subgroup of patients with baseline HbA_{1c} > 8% and were comparable with vildagliptin (−0.92% [SE: 0.08%]) and glimepiride (−0.95% [SE: 0.07%]; figure 3) treatment. A similar proportion of patients also reached the HbA_{1c} target of <7% in each treatment group (54.1 and 55.5% respectively). By contrast, the proportion of patients achieving the HbA_{1c} target without hypoglycaemia was significantly greater in the vildagliptin group (50.9%) than in the glimepiride group (44.3%; p = 0.006). Mean [SE] FPG decreased from baseline to week 52 by a similar extent in both groups (−1.01 [0.06] mmol/l with vildagliptin and −1.14 [0.06] mmol/l with glimepiride; not significant).

The overall incidence of confirmed hypoglycaemia was nearly 10-fold lower in patients receiving vildagliptin (one or more hypoglycaemic event was reported by 1.7% of patients receiving vildagliptin and by 16.2% of patients receiving glimepiride) with 14-fold fewer confirmed hypoglycaemic episodes in the vildagliptin group (39 vs. 544 episodes, respectively; p < 0.01). No severe hypoglycaemia occurred in any patients receiving vildagliptin compared with in 10 patients taking glimepiride (p < 0.01; figure 4). Furthermore, no patients receiving vildagliptin discontinued due to hypoglycaemia, compared with 11 patients in the glimepiride group. In the subgroup achieving HbA_{1c} target <7% at endpoint, the proportion of patients experiencing ≥1 hypoglycaemic event was also 10-fold lower with vildagliptin than with glimepiride (1.9% and 18.9% respectively). *Post hoc* analyses by age group also revealed a benefit with vildagliptin in the elderly (>65 years, n = 712, mean age of 68.4 years), with 10-fold fewer elderly patients experiencing a hypoglycaemic event in the vildagliptin group than in the glimepiride group (1.7 vs. 16.4% of patients respectively).

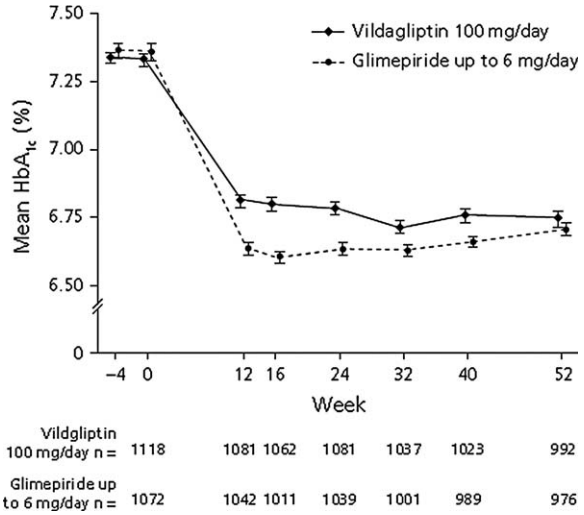

Fig. 2 Mean glycosylated haemoglobin (HbA_{1c}) by treatment and visit (censored at start of rescue medication) for the per protocol population.

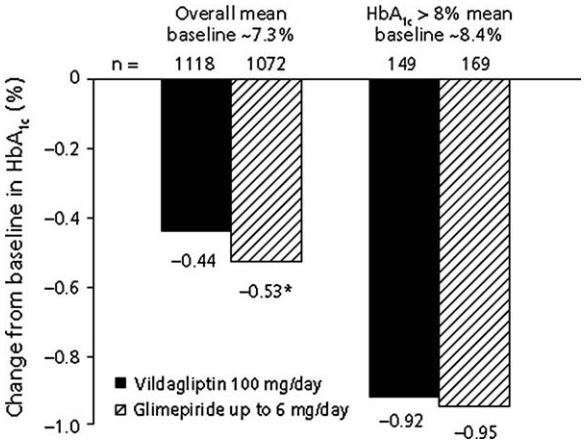

Fig. 3 Mean glycosylated haemoglobin (HbA_{1c}) reduction at week 52 endpoint in the overall population (PP) and in the baseline $HbA_{1c} > 8\%$ subgroup. *denotes non inferiority.

Body weight at baseline averaged 89.01 and 88.62 kg in the vildagliptin and glimepiride groups respectively. It did not change during 52 weeks of treatment with vildagliptin (adjusted mean [SE] change from baseline −0.23 [0.11] kg) but increased with glimepiride (adjusted mean [SE] change from baseline +1.56 [0.12] kg). The mean between-group difference was statistically significant (−1.79 [0.16] kg; $p < 0.001$). From similar baseline levels, all fasting lipid parameters improved with vildagliptin compared with glimepiride. The magnitudes of the changes were modest (<10% from baseline) but triglyceride, total cholesterol, non-high-density lipoprotein cholesterol and very low-density lipoprotein cholesterol levels all significantly decreased relative to glimepiride over 52 weeks in patients receiving vildagliptin ($p < 0.01$ for all).

Safety and Tolerability Profile

During the 52-week treatment period, one or more AE was reported by 74.5 and 81.1% of patients receiving vildagliptin and glimepiride respectively (table 2). The most commonly reported AEs (>5% in any group) were nasopharyngitis, headache, dizziness, influenza, diarrhoea, back pain, fatigue, asthenia, tremor, hyperhidrosis, nausea, hunger and hypoglycaemia. The overall safety profile of vildagliptin was similar to that of

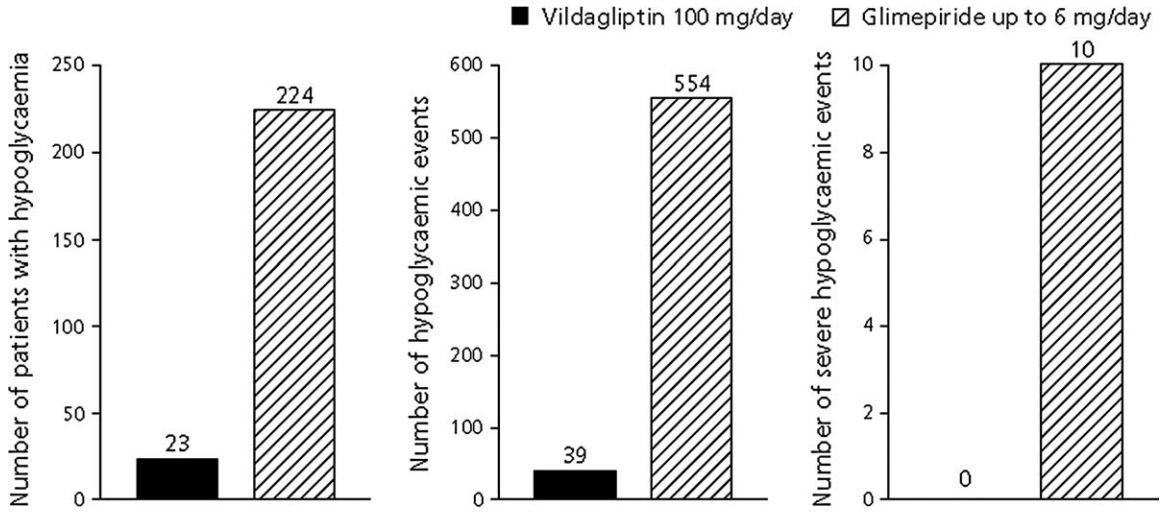

Fig. 4 Incidence and severity of hypoglycaemic events with vildagliptin and glimepiride during the 52-week treatment period (safety population).

glimepiride with the important exception of all hypoglycaemia-related AEs which were reported more frequently in the glimepiride group: tremor (20% in the glimepiride group vs. 3.7% in the vildagliptin group), hyperhidrosis (17.4 vs. 3.3%), dizziness (13.6 vs. 6.6%), asthenia (10.4 vs. 3.8%) and hunger (5.1 vs. 0.7%). These AEs contributed greatly to the higher incidence of drug-related AEs reported with glimepiride (35.7 vs. 17.6% with vildagliptin).

Discontinuation because of AEs was lower in the vildagliptin (5.0%) than in the glimepiride (8.0%) group, as was the incidence of serious AEs (7.1 vs. 9.5%). The incidence of CCV events confirmed by the CCV adjudication committee was 0.9% with vildagliptin and 1.6% with glimepiride. This corresponded to a total of 12 events in the vildagliptin group occurring in 12 patients and 22 in the glimepiride group occurring in 22 patients, as detailed in table 3. No major changes from baseline to endpoint or between-treatment differences were observed for any haematological or biochemical parameters, and the proportion of patients experiencing notable abnormalities in any biochemical or haematological variables was also comparable between treatment groups.

Five deaths were reported during the study (two in the vildagliptin group and three in the glimepiride group), none of which were suspected to be treatment related.

Table 2 Overall safety summary and most common adverse events (AEs)

	Vildagliptin (50 mg twice daily) n = 1389, n (%)	Glimepiride (up to 6 mg/day) n = 1383, n (%)
Overall safety summary		
Any AE	1035 (74.5)	1121 (81.1)
Discontinuation because of AEs	69 (5.0)	111 (8.0)
Drug-related AEs	244 (17.6)	494 (35.7)
Serious AEs	99 (7.1)	132 (9.5)
Adjudicated CCV AEs	12 (0.9)	22 (1.6)
Hypoglycaemia	23 (1.7)	224 (16.2)
Deaths	2 (0.1)	3 (0.2)
Most common AEs		
Nasopharyngitis	131 (9.4)	129 (9.3)
Headache	106 (7.6)	109 (7.9)
Dizziness	91 (6.6)	188 (13.6)
Influenza	79 (5.7)	60 (4.3)
Diarrhoea	76 (5.5)	71 (5.1)
Back pain	75 (5.4)	71 (5.1)
Fatigue	57 (4.1)	90 (6.5)
Nausea	56 (4.0)	71 (5.1)
Asthenia	53 (3.8)	144 (10.4)
Tremor	52 (3.7)	276 (20.0)
Hyperhidrosis	46 (3.3)	240 (17.4)
Hypoglycaemia	23 (1.7)	224 (16.2)
Hunger	10 (0.7)	71 (5.1)

CCV, cardiovascular and cerebrovascular.
For most common AEs, the n (%) of patients reporting common AEs up to and including the week 52 visit (≥5% in any group) by preferred term (safety population) are detailed.
All events were included in analysis regardless of rescue medication use.

Discussion

Vildagliptin 50 mg twice daily added to metformin was non-inferior to glimepiride (mean dose 4.5 mg/day) after 52 weeks of treatment. Furthermore, the combination of vildagliptin and metformin did not promote weight gain and offered clear advantages in terms of a reduction in the incidence of hypoglycaemia. Vildagliptin therefore represents an appealing therapeutic option in patients with T2DM who fail to meet target HbA_{1c} with metformin monotherapy, particularly those with mild hyperglycaemia, and older or more fragile individuals who are more susceptible to hypoglycaemia.

The present study demonstrated that vildagliptin has a favourable AE profile compared with glimepiride with respect to hypoglycaemia – patients in the vildagliptin group experienced a 10-fold lower incidence of confirmed hypoglycaemia and 14-fold fewer episodes of hypoglycaemia than did those in the glimepiride group. Notably, this held true in the elderly subpopulation and in patients achieving an HbA_{1c} below 7% at endpoint; both groups who are at an even higher risk of hypoglycaemia. In addition, fewer patients in the vildagliptin group experienced CCV events confirmed by the adjudication committee (0.9%) than did those in the glimepiride group (1.6%), in line with a recent pooled analysis showing a favourable CV profile of vildagliptin vs. placebo and all comparators [20].

Table 3 Number (%) of patients with clinically significant adverse events confirmed by the cardiovascular and cerebrovascular (CCV) adjudication committee up to and including the week 52 visit (safety population)

CCV event category	Vildagliptin (50 mg twice daily) n = 1389, n (%)	Glimepiride (up to 6 mg/day) n = 1383, n (%)
Any CCV event	12 (0.9)	22 (1.6)
Acute coronary syndrome	5 (0.4)	7 (0.5)
Cardiac arrhythmia	3 (0.2)	5 (0.4)
Congestive heart failure	2 (0.1)	2 (0.1)
Death	2 (0.1)	1 (0.1)
Peripheral vascular disease	0 (0.0)	1 (0.1)
Stroke	0 (0.0)	7 (0.5)
Syncope	1 (0.1)	0 (0.0)

Two recently published studies have examined the effects of intensive lowering of blood glucose levels on CV risk in patients with T2DM [21,22], and both found that near-normal glycaemic control (median HbA_{1c} of 6.4% at study end in the intensive group) did not reduce the incidence of CV events within a 3.5- to 5-year time frame. The unanticipated finding from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was that overall and CV mortality were greater in the intensive group [21]. Indeed, 19 of the 41 unexpected excess deaths from CV causes in the ACCORD study were attributed to 'unexpected or presumed CV disease', which were possibly related to or precipitated by severe hypoglycaemia [21]. Interestingly, in the ACCORD study, previous occurrence of severe hypoglycaemia was one of the strongest predictors for a primary CV event regardless of treatment arm.

Given the potential CV risk associated with severe hypoglycaemia, it would therefore be prudent to use therapies that are associated with a low risk of hypoglycaemia to manage strict glycaemic control in patients with T2DM [23]. Very recent findings from a 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) show sustained legacy effects of improved glucose control early on in the disease (in newly diagnosed patients) and indicate an emergent long-term benefit on CV risk observed only with extended post-trial follow-up, strengthening the rationale for attaining early and optimal glycaemic control [24].

A previous 1-year study comparing the efficacy of sitagliptin or glipizide added to metformin showed similar results to the present study, demonstrating comparable efficacy, less weight gain and a lower risk of hypoglycaemia with sitagliptin than with glipizide [25]. However, the study had several limitations, which were avoided in the present study: (i) the glipizide dose was suboptimal (mean dose:10.3 mg/day in the PP population); (ii) only 67.7% of the randomized population were included in the PP analysis, mainly because of missing data at week 52, with greater discontinuation owing to a lack of efficacy with sitagliptin (15%) than glipizide (10%); and (iii) patients on various oral regimens were eligible to enter the study following a metformin titration–stabilization period (compared with an average duration of 36 months metformin monotherapy in the present study). Nevertheless, the two studies together suggest that DPP-4 inhibitors may represent a preferred add-on therapy when metformin alone fails in patients with T2DM.

In current practice, an SU or TZD are used as an add-on to metformin to reach or maintain HbA_{1c} below target levels [26]. As glycaemic targets are lowered further, many patients with T2DM become at risk of having inadequate glycaemic control because of the limitations of currently available antidiabetic agents (e.g. to avoid the increased risk of hypoglycaemia with SUs and the weight gain with TZDs) [27,28]. Vildagliptin displays robust efficacy with the added benefits of a much lower risk of hypoglycaemia and no weight gain, making it a promising alternative to SUs and TZDs as add-on therapy to metformin.

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