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Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial

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Aim: To compare the efficacy and safety of sitagliptin vs. glipizide in patients with type 2 diabetes and inadequate glycaemic control [haemoglobin A_{1c} (HbA_{1c}) $\geq$ 6.5 and $\leq$10%] on metformin monotherapy.
Methods: After a metformin dose titration/stabilization period ($\geq$1500 mg/day), 1172 patients were randomized to the addition of sitagliptin 100 mg q.d. (N = 588) or glipizide 5 mg/day (uptitrated to a potential maximum 20 mg/day) (N = 584) for 52 weeks. The primary analysis assessed whether sitagliptin was non-inferior to glipizide regarding HbA_{1c} changes from baseline at Week 52 using a per-protocol approach.
Results: From a mean baseline of 7.5%, HbA_{1c} changes from baseline were −0.67% at Week 52 in both groups, confirming non-inferiority. The proportions achieving an $HbA_{1c} < 7\%$ were 63% (sitagliptin) and 59% (glipizide). Fasting plasma glucose changes from baseline were −0.56 mmol/l (−10.0 mg/dl) and −0.42 mmol/l (−7.5 mg/dl) for sitagliptin and glipizide, respectively. The proportion of patients experiencing hypoglycaemia episodes was significantly ($p < 0.001$) higher with glipizide (32%) than with sitagliptin (5%), with 657 events in glipizide-treated patients compared with 50 events in sitagliptin-treated patients. Sitagliptin led to weight loss (change from baseline = −1.5 kg) compared with weight gain (+1.1 kg) with glipizide [between-treatment difference (95% confidence interval) = −2.5 kg (−3.1, −2.0); $p < 0.001$].
Conclusions: In this study, the addition of sitagliptin compared with glipizide provided similar HbA_{1c}-lowering efficacy over 52 weeks in patients on ongoing metformin therapy. Sitagliptin was generally well tolerated, with a lower risk of hypoglycaemia relative to glipizide and with weight loss compared with weight gain with glipizide.
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Introduction

Patients with type 2 diabetes have multiple defects contributing to hyperglycaemia including insulin resistance, inadequate insulin secretion and excessive hepatic glucose production. Oral antihyperglycaemic agents (OHA) that target any of these metabolic defects will improve glucose levels [1]. Metformin, the most commonly prescribed OHA, targets excessive hepatic glucose output and insulin resistance [2,3]. While defective at the time

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of diagnosis, β-cell function continues to deteriorate over time in patients with type 2 diabetes, leading to progressive failure of insulin secretion. This progressive loss of β-cell function may explain why many patients who initially achieve glycaemic control fail to maintain control at levels consistent with current guidelines [e.g. haemoglobin A_{1c} (HbA_{1c}) < 7 or <6.5%] and hence require additional therapies [4]. Sulfonylureas, which act as insulin secretagogues, are the most common next therapeutic step when patients do not achieve or maintain glycaemic control on metformin [5]. Glycaemic efficacy is similar across sulfonylurea agents [5,6]. Sulfonylurea stimulation of insulin secretion is not strictly glucose dependent [6]. Although generally well tolerated, these agents are associated with hypoglycaemia because of continued stimulation of insulin secretion with falling glucose concentrations [7]. Weight gain is another common side effect of sulfonylurea treatment, potentially related to the sulfonylurea-induced increase in insulin concentrations [1]. An agent that can provide efficacy similar to a sulfonylurea but with a better safety profile could provide a useful alternative.

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a novel treatment for type 2 diabetes that improves glycaemic control through a new mechanism, enhancement of the incretin axis [8–10]. Sitagliptin inhibits the enzymatic degradation and inactivation of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [11,12]. These incretins augment glucose-induced insulin secretion after meals. In addition, GLP-1 suppresses glucagon release, delays gastric emptying and increases satiety [13–15]. Notably, incretin-induced stimulation of insulin release and the suppression of glucagon release by GLP-1 occur in a glucose-dependent fashion. Studies have shown, for example that at normal or elevated glucose levels, GLP-1 potently stimulates insulin secretion and inhibits glucagon release – effects that disappear when glucose levels approach normal concentrations [16]. Single doses of sitagliptin have been shown to increase active GLP-1 and GIP levels, enhance insulin secretion and suppress glucagon release in patients with type 2 diabetes [8]. In prior clinical studies, sitagliptin added to ongoing metformin monotherapy significantly improved fasting and postprandial glycaemic control and measures of β-cell function in patients with type 2 diabetes [17,18]. Moreover, in these trials, sitagliptin was well tolerated with a neutral effect on body weight and a low risk of hypoglycaemia and gastrointestinal adverse experiences. The present 52-week study in patients with type 2 diabetes with inadequate glycaemic control on metformin monotherapy was designed to compare the glycaemic efficacy and safety of the addition of sitagliptin with that of a standard sulfonylurea agent, glipizide.

Patients and Methods

Patients

Patient Selection Criteria

The screening/eligibility run-in period, described below, was designed to allow patients with type 2 diabetes on a variety of different regimens at screening to participate. Men and women (age 18–78 years) with type 2 diabetes who were not currently on an OHA, were taking any OHA in monotherapy or were taking metformin in combination with another OHA were potentially eligible to participate in the study if they all met screening criteria. Patients were excluded if they had a history of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with the use of metformin or a fasting plasma glucose (FPG) (or a fasting fingerstick glucose) at or just prior to randomization >15.0 mmol/l (270 mg/dl). Other treatments for hyperglycaemia were prohibited during the study. Concurrent lipid lowering and antihypertensive medications, thyroid medications, hormone replacement therapy and birth control medications were allowed but were expected to remain at stable doses. Patients received counselling on exercise and a diet consistent with American Diabetes Association recommendations throughout the study.

All patients provided written informed consent to participate, and the study protocol was reviewed and approved by the appropriate committees and authorities for each study site. The study was performed in accordance with the Declaration of Helsinki.

Study Design

This was a multinational, randomized, parallel-group, non-inferiority study with an active-controlled, double-blind treatment period (Sitagliptin Protocol 024; Clinical Trials.gov NCT00094770). A non-inferiority design was chosen as a standard approach to assess similarity of a new agent to a standard therapy. Patients who were already on metformin ≥1500 mg/day and had an $HbA_{1c} \geq 6.5$ and ≤10% directly entered a 2-week placebo run-in period and were eligible to be randomized. Patients not currently on an OHA, patients on an OHA other than metformin monotherapy at a dose ≥1500 mg/day or patients on metformin in combination with another OHA entered a metformin monotherapy treatment titration and dose-stable period of at least 8 weeks.

Patients with an HbA_{1c} ≥6.5 and ≤10% after the metformin dose-stable period entered a 2-week single-blind placebo run-in period. Following this 2-week period, eligible patients had baseline measurements and then were randomized in a 1 : 1 ratio to the addition of sitagliptin 100 mg once daily or glipizide (at an initial dose of 5 mg/day). After the starting dose of 5 mg/day, glipizide was uptitrated according to protocol-specified criteria to a potential maximum dose of 20 mg/day. In 3-week intervals during the first 18 weeks of treatment, glipizide was uptitrated if premeal fingerstick glucose values were >6.1 mmol/l (110 mg/dl). At the investigator's discretion, uptitration of glipizide was withheld if the investigator considered that uptitration would place the patient at risk for hypoglycaemia. At any time during the study, glipizide could be downtitrated to prevent recurrent hypoglycaemic events.

Study Evaluations

Efficacy Assessments

After an overnight fast, blood was collected for the assessment of HbA_{1c}, FPG, insulin, proinsulin and lipid parameters [total cholesterol (TC), low-density lipoprotein–cholesterol (LDL-C), triglycerides (TGs), high-density lipoprotein–cholesterol (HDL-C) and non-HDL-C] at baseline and at various time points during the study. Homeostasis model assessment-β cell function (HOMA-β) and the proinsulin/insulin ratio were used to assess aspects of β-cell function [19,20]. HOMA-insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated to assess changes in insulin resistance [20,21]. As a prespecified analysis, durability of treatments was evaluated by comparing the rate of rise in HbA_{1c} from Week 24 to Week 52.

Safety Assessments

Data on adverse experiences, physical examinations, vital signs, ECGs and body weight were collected throughout the study. All adverse experiences were rated by the study site investigators for intensity and relationship to study drug. Laboratory safety evaluations included blood chemistry, haematology and urinalysis. Patients experiencing symptoms of hypoglycaemia were instructed to obtain a fingerstick glucose, record the value in a log book and contact their study site. Patients were discontinued for lack of efficacy based on progressively stricter glycaemic criteria: from randomization through Week 6 for patients on two tablets (5-mg tablets) of glipizide/glipizide placebo for at least 2 weeks, FPG > 14.4 mmol/l (270 mg/dl); from Week 6 through Week 12 for patients on maximal dose (four 5-mg tablets) of glipizide/glipizide placebo for at least 2 weeks, FPG > 13.3 mmol/l (240 mg/dl); from Week 12 through Week 18 for patients on maximal dose of glipizide/glipizide placebo for at least 2 weeks, FPG > 12.2 mmol/l (220 mg/dl); from Week 18 through Week 30, FPG > 11.1 mmol/l (220 mg/dl) and from Week 30 to Week 52, HbA_{1c} > 8.0%.

All laboratory efficacy and safety measurements and ECGs were performed at central laboratories (PPD Global Central Labs, LLC, Highland Heights, KY, USA, and Zaventem, Belgium; Covance Central Diagnostics, Inc., Reno, NV, USA). HbA_{1c} was determined by high-performance liquid chromatography (Tosoh A1c 2.2; Tosoh Medics, Foster City, CA, USA). Plasma glucose was determined by the hexokinase method (Roche Diagnostics, Basel, Switzerland). Serum insulin was determined using chemiluminescence assay (Elecsys 2010; Roche Diagnostics). Serum proinsulin was determined using an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). TG was measured by enzymatic determination of glycerol (Roche Diagnostics). After selective removal of apolipoprotein B–containing lipoproteins by heparin and manganese chloride precipitation for HDL isolation, HDL-C and TC were quantified enzymatically (Roche Diagnostics). LDL-C level was calculated using the Friedewald equation [22]. Non-HDL-C level was calculated by subtracting HDL-C level from TC.

Statistical Analyses

The primary efficacy analysis assessed whether the study treatments were non-inferior with regard to the HbA_{1c} change from baseline at Week 52 using a per-protocol (PP) approach [23]. The PP population consists of patients who completed all 52 weeks of treatment and did not have any reasons for exclusion from this population, including no baseline data, no treatment data at Week 52 or major protocol violations (e.g. drug compliance <75%, change in metformin dose, addition of non-study OHA, incorrect double-blind study medication). For change from baseline in HbA_{1c}, sitagliptin was considered non-inferior to glipizide if the upper boundary of the two-sided 95% confidence interval (CI) for the mean difference between sitagliptin and glipizide was less than the margin, $\delta = 0.3\%$. This margin was selected so that for non-inferiority to be declared (i.e. for the upper boundary of the confidence interval to be less than the selected margin), the between-group difference observed would be small. An analysis of covariance

model was used to compare the treatment groups for efficacy endpoints, focusing on change from baseline at Week 52, with baseline values and prior OHA status as covariates. The difference between sitagliptin and glipizide for efficacy endpoints was assessed by testing the difference in the least squares (LS) mean change (or mean per cent change) from baseline at Week 52. Additional efficacy analyses were based on the all patients–treated (APT) population that consisted of all randomized patients who received at least one dose of study treatment and who had both a baseline and at least one post-baseline measurement; missing values in the APT analysis were handled by the last observation carried forward approach.

The durability of HbA_{1c} lowering was compared between treatments by evaluating the coefficient of durability (COD), defined as the rate of rise in HbA_{1c} from Week 24 to Week 52. The proportion of patients achieving an $HbA_{1c} < 7$ or $<6.5\%$ was compared between treatments using a logistic regression analysis. Subgroup analyses for the primary efficacy endpoint (i.e. change from baseline in HbA_{1c} at Week 52) were performed in subgroups defined by baseline HbA_{1c} categories (<7, 7% to <8, 8% to <9, $\geq 9\%$).

Safety and tolerability were evaluated by a review of safety parameters including adverse experiences, laboratory safety parameters, body weight, vital signs and ECG data from the all-patients-as-treated population, which was defined as all randomized patients who received at least one dose of study medication. For body weight change and the prespecified clinical adverse experiences of hypoglycaemia and specific gastrointestinal adverse experiences (abdominal pain, nausea, vomiting and diarrhoea), inferential testing was performed for between-group comparisons. Compliance was assessed by tablet count.

Results

Patient Disposition and Characteristics

Of the 1172 randomized patients, 793 were included in the PP analysis (sitagliptin, n = 382 and glipizide, n = 411) (figure 1). Of the 379 patients excluded from the PP analysis, 96% were excluded because of missing treatment data at Week 52. More patients in the sitagliptin group discontinued treatment compared with those in the glipizide group (figure 1); this difference was mainly because of a higher number of sitagliptin-treated patients discontinuing for lack of efficacy, which was based on prespecified FPG and/or HbA_{1c} criteria throughout the treatment period. Patients who discontinued because of lack of efficacy had more severe hyperglycaemia at baseline than those who completed the study (baseline HbA_{1c}: 8.6 vs. 7.5%, respectively); discontinued patients also tended to be slightly older than patients who completed the study (57 vs. 55 years, respectively) and had a slightly more body weight (93 vs. 90 kg, respectively).

The mean dose of glipizide was 10.3 mg/day in the PP population. Approximately 58% of patients reached a final dose of at least 10 mg/day (22% reached a final dose of 20 mg/day), while because downtitration was permitted for recurrent hypoglycaemia, 10% of patients were not taking glipizide at study end. For the APT population, the mean dose of glipizide was 10.6 mg/day. For all patients, the mean duration of exposure to study drug was slightly greater in the sitagliptin group [297.1 days (42.4 weeks)] than in the glipizide group [287.5 days (41.1 weeks)]. The mean (s.d.) compliance rates were 98.6% (3.8) and 98.3% (3.6) in the sitagliptin and glipizide groups, respectively.

Treatment groups were generally well balanced for baseline demographics and efficacy variables for all randomized patients (table 1). In the PP population, the baseline demographics and efficacy variables were similar to those of the randomized population results, with an average duration of known diabetes of 5.8 years, 70% on an OHA monotherapy at screening, and a mild-to-moderate degree of hyperglycaemia with a mean HbA_{1c} of 7.5% (range = 5.8–10.1%; 73% of patients with an $HbA_{1c} < 8.0\%$) and mean FPG of 8.8 mmol/l (158 mg/dl).

Efficacy

In the PP population, the LS mean HbA_{1c} change from baseline at Week 52 was −0.67% in both the sitagliptin and the glipizide treatment groups (table 2). The upper limit of the two-sided 95% CI for the between-group LS mean difference (0.08%) was less than the prespecified non-inferiority margin of 0.3%, satisfying the primary hypothesis of non-inferiority of sitagliptin to glipizide in lowering HbA_{1c} when co-administered with metformin. In the APT population, LS mean HbA_{1c} change from baseline at Week 52 was similar in the two treatment groups: −0.51% (95% CI: −0.60, −0.43) with sitagliptin and −0.56% (−0.64, −0.47) with glipizide [between-group difference in LS mean change from baseline (95% CI) = 0.04% (−0.04, 0.13)]. This minimal between-group difference supported the PP results regarding non-inferiority of sitagliptin to glipizide. Although treatment with glipizide provided greater initial HbA_{1c} lowering, with the maximum between-group

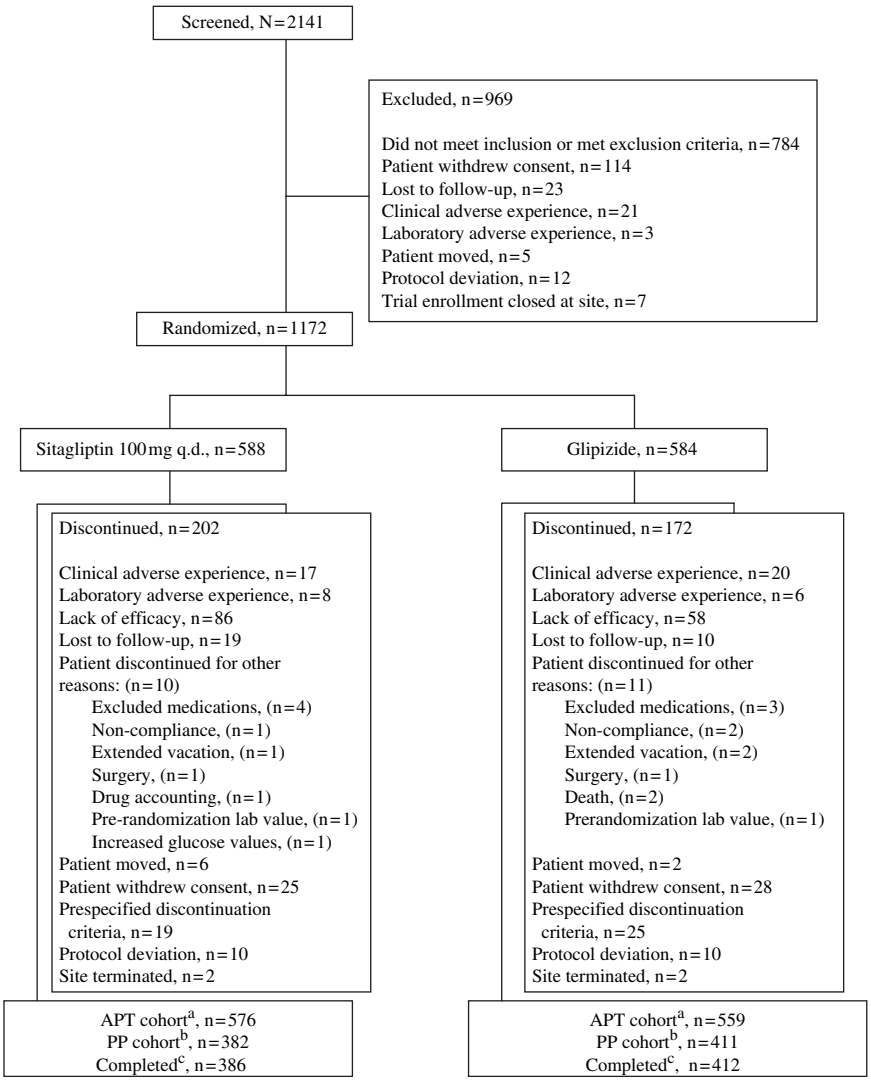

Fig. 1 Patient disposition at each stage of the study.[a]All patients–treated (APT) cohort includes randomized patients who received at least one dose of study treatment and who had both a baseline and at least one post-baseline measurement. [b]Per-protocol (PP) cohort includes randomized patients who completed all 52 weeks of treatment and did not have any reasons for exclusion from this population, including no baseline data, no treatment data at Week 52 or major protocol violations. [c]Completer population includes randomized patients who completed all 52 weeks of treatment.

difference observed at Week 24 (figure 2A), treatment with sitagliptin was significantly more durable (i.e. smaller rise in HbA_{1c} from Week 24 to Week 54) than that with glipizide [COD (95% CI): 0.008%/week (0.005, 0.010) vs. 0.011%/week (0.008, 0.013), respectively; between-group difference in COD (95% CI) = −0.003 (−0.005, −0.001)].

In the PP population, the percentage of patients with an $HbA_{1c} < 7\%$ at Week 52 was similar between the sitagliptin (63%; n/N = 240/382) and the glipizide (59%; 242/411) groups [difference in proportion (95% CI) = 3.9% (−2.8, 10.7)]. In both groups, 29% of the patients reached an $HbA_{1c} < 6.5\%$ [difference in proportion (95% CI) = −0.1% (−6.4, 6.2)]. In the APT population at Week 52, 52 and 51% of patients had an $HbA_{1c} < 7\%$ [difference in proportion (95% CI) = 0.9% (−4.9, 6.7)], and 24 and 25% had an $HbA_{1c} < 6.5\%$ [difference in proportion (95% CI) = −0.7% (−5.7, 4.3)] in the sitagliptin and glipizide groups, respectively.

A subgroup analysis of HbA_{1c} response by baseline HbA_{1c} levels showed an increase in treatment effects for both treatment groups, with increasing baseline HbA_{1c}

Table 1 Baseline demographics and efficacy endpoint data for all randomized patients*

Characteristic	Sitagliptin 100 mg q.d. + metformin (N = 588)	Glipizide + metformin (N = 584)
Age (years)	56.8 (9.3)	56.6 (9.8)
Sex, n (%)		
Male	336 (57.1)	358 (61.3)
Female	252 (42.9)	226 (38.7)
Race, n (%)		
Caucasian	432 (73.5)	434 (74.3)
Black	41 (7.0)	35 (6.0)
Hispanic	43 (7.3)	46 (7.9)
Asian	50 (8.5)	49 (8.4)
Other	22 (3.7)	20 (3.4)
Body weight (kg)	89.5 (17.4)	89.7 (17.5)
Body mass index (kg/m^2)	31.2 (5.0)	31.3 (5.2)
Duration of diabetes mellitus (years)	6.5 (6.1)	6.2 (5.4)
Use of OHA at screening, n (%)		
Dual therapy	177 (30.1)	159 (27.2)
Monotherapy	386 (65.6)	397 (68.0)
Absence	25 (4.3)	28 (4.8)
HbA_{1c}, % (range)	7.7 (0.9) (6.1–11.0)	7.6 (0.9) (5.8–10.5)
HbA_{1c} distribution at baseline, n (%)		
$HbA_{1c} < 8\%$	375 (64.0)	381 (65.5)
$HbA_{1c} \geq 8$ to $<9\%$	151 (25.8)	141 (24.2)
$HbA_{1c} \geq 9\%$	60 (10.2)	60 (10.3)
FPG (mmol/l)	9.2 (2.3)	9.1 (2.3)

FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin A_{1c}; OHA, oral antihyperglycaemic agent.

*Data are expressed as mean (±s.d.) or frequency [n (%)], unless otherwise indicated. To convert FPG in mmol/l to mg/dl, multiply by 18.

levels. In the PP population, the change in HbA_{1c} from baseline was similar between treatments within each baseline HbA_{1c} stratum with the greatest effect observed in patients with baseline $HbA_{1c} \geq 9.0\%$ [mean change from baseline (s.e.) = −1.68% (0.16) with sitagliptin and −1.76 (0.13) with glipizide; figure 2B]. In the APT population, the mean change in HbA_{1c} from baseline was also similar between treatments within each baseline HbA_{1c} stratum, except for the results in the highest baseline HbA_{1c} stratum (≥9%). In this stratum, the change from baseline was numerically greater in the glipizide group (−1.31%) than in the sitagliptin group (−0.94%).

In the PP population, the maximal FPG effect was observed at Week 24 for both treatments, followed by a rise in FPG through Week 52 (figure 3). The LS mean FPG change from baseline at Week 52 was not different between groups (table 2). At Week 52, the sitagliptin group showed a numerically smaller increase from baseline in fasting insulin compared with the glipizide group (table 2). There was a decrease from baseline in fasting proinsulin and the proinsulin/insulin ratio at Week 52 in the sitagliptin group; however, the glipizide group had an increase from baseline in these two endpoints at Week 52 (table 2). The sitagliptin group had a smaller increase in HOMA-β than the glipizide group. No meaningful changes in HOMA-IR were found at Week 52, although QUICKI was significantly increased from baseline with sitagliptin relative to glipizide (table 2). No between-group differences were observed for any measured lipid parameter, except for HDL-C, in which a significant increase from baseline was found with sitagliptin (3.7%) compared with glipizide (1.2%) [between-group difference in LS mean per cent change from baseline (95% CI) = 2.5% (0.6, 4.3)].

Safety and Tolerability

When added to ongoing metformin therapy, there were no meaningful differences between groups in the incidence of overall clinical adverse experiences or clinical adverse experiences that were assessed as serious or leading to discontinuation (table 3). The proportion of patients experiencing adverse experiences considered related to study drug by the investigator was higher with glipizide than with sitagliptin (30.3 vs. 14.5%, respectively), related to a higher incidence of hypoglycaemia observed with glipizide treatment. There were two serious adverse experiences considered related to study drug by the investigator in the glipizide group (myocardial infarction and spontaneous abortion) and none in the sitagliptin group. Three deaths occurred in this 52-week study, two in the glipizide group (sudden cardiac death and myocardial infarction) and one in the sitagliptin group (because of trauma) (table 3); none was considered related to study drug. The incidence of adverse experiences by body systems was comparable between the sitagliptin and the glipizide treatment groups. There was a slightly higher incidence of adverse experiences in the sitagliptin group than in the glipizide group for fatigue (3.1 vs. 0.9%), dizziness (3.7 vs. 2.1%), nasopharyngitis (10.5 vs. 7.5%), sinusitis (3.2 vs. 1.9%), urinary tract infection (5.4 vs. 2.7%), osteoarthritis (2.6 vs. 0.7%) and pain in extremity (3.4 vs. 1.4%). In general, most of these events were rated as mild in intensity, not related to study drug, and resolved while patients continued in the study. The incidence of overall gastrointestinal events was similar in the sitagliptin and glipizide groups (20.4 vs. 19.3%, respectively) and the incidence of prespecified gastrointestinal events [abdominal pain, diarrhoea, nausea and vomiting (table 3)] was not significantly different between groups.

Table 2 Key efficacy results in the per-protocol population*

	n	Week 0 (baseline), mean (s.d.)	Week 52, mean (s.d.)	LS mean change from baseline (95% CI)	Difference in LS mean change (95% CI)
HbA_{1c} (%)					
Glipizide + metformin	411	7.52 (0.85)	6.86 (0.69)	−0.67 (−0.75, −0.59)	−0.01 (−0.09, 0.08)
Sitagliptin + metformin	382	7.48 (0.76)	6.84 (0.66)	−0.67 (−0.75, −0.59)	
Fasting plasma glucose (mmol/l)					
Glipizide + metformin	407	8.84 (2.14)	8.22 (2.20)	−0.42 (−0.67, −0.17)	−0.14 (−0.38, 0.11)
Sitagliptin + metformin	382	8.75 (1.87)	8.04 (1.84)	−0.56 (−0.81, −0.30)	
Fasting serum insulin (pmol/l)					
Glipizide + metformin	393	80.4 (63.0)	83.4 (51.6)	6.6 (0.6, 12.6)	−5.4 (−11.4, 0.6)
Sitagliptin + metformin	374	79.8 (72.6)	78.0 (54.0)	1.8 (−4.8, 7.8)	
Fasting serum proinsulin (pmol/l)					
Glipizide + metformin	400	26.3 (26.5)	29.7 (24.2)	3.8 (1.3, 6.2)	−6.3 (−8.7, −3.8)
Sitagliptin + metformin	371	25.5 (24.1)	22.9 (21.1)	−2.5 (−5.1, 0.1)	
Proinsulin/insulin ratio					
Glipizide + metformin	388	0.341 (0.193)	0.364 (0.201)	0.033 (0.009, 0.057)	−0.048 (−0.072, −0.025)
Sitagliptin + metformin	365	0.334 (0.198)	0.310 (0.218)	−0.016 (−0.040, 0.009)	
HOMA-β (%)					
Glipizide + metformin	387	57.0 (48.5)	74.3 (75.8)	14.0 (6.5, 21.5)	−10.4 (−18.0, −2.8)
Sitagliptin + metformin	368	57.6 (51.9)	64.4 (46.3)	3.6 (−4.1, 11.3)	
HOMA-IR					
Glipizide + metformin	388	5.3 (4.6)	5.1 (3.5)	0.2 (−0.3, 0.6)	−0.3 (−0.7, 0.2)
Sitagliptin + metformin	368	5.2 (5.4)	4.8 (3.8)	−0.1 (−0.5, 0.4)	
QUICKI (insulin sensitivity)					
Glipizide + metformin	388	0.314 (0.033)	0.313 (0.028)	−0.003 (−0.006, 0.000)	0.005 (0.002, 0.008)
Sitagliptin + metformin	368	0.313 (0.029)	0.317 (0.031)	0.002 (−0.001, 0.005)	

CI, confidence interval; FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment-β cell function; HOMA-IR, HOMA-insulin resistance; LS, least squares.

*To convert FPG in mmol/l to mg/dl, multiply by 18.

[correction added after online publication 23 January 2007: column 4, values were rearranged; column 5, value was corrected]

There were 187 (32.0%) glipizide-treated patients who reported 657 episodes of hypoglycaemia compared with 29 (4.9%) sitagliptin-treated patients who reported 50 episodes of hypoglycaemia (table 3). Patients were instructed to collect fingerstick glucose values if possible when hypoglycaemia symptoms occurred. In 598 episodes in the glipizide group, fingerstick values were obtained, of which 435 (73%) were <3.9 mmol/l (70 mg/dl). For sitagliptin, 43 episodes had fingerstick glucose values, and 31 (72%) of these episodes had values <3.9 mmol/l (70 mg/dl). Eight patients (1.4%) on glipizide had a hypoglycaemic episode that required non-medical assistance but did not exhibit marked severity (i.e. markedly depressed level of consciousness, loss of consciousness or seizure) compared with one patient (0.2%) on sitagliptin, while seven patients (1.2%) in the glipizide group had an episode that required medical assistance or exhibited marked severity compared with one patient (0.2%) in the sitagliptin group.

At 52 weeks, body weight was significantly reduced with sitagliptin [LS mean change from baseline (95% CI) = −1.5 kg (−2.0, −0.9)] and significantly increased with glipizide [1.1 kg (0.5, 1.6)] relative to baseline, with a between-treatment difference of −2.5 kg (−3.1, −2.0; $p < 0.001$) (figure 4). The changes in body weight for each group were consistent with changes in waist circumference: a mean (±s.d.) decrease from baseline of −1.4 cm (±5.8) was measured for the sitagliptin group compared with a mean (±s.d.) increase from baseline of 0.7 cm (±6.0) in the glipizide group [between-group difference in LS mean change from baseline (95% CI) = −2.1 cm (−2.8, −1.3)].

There were no clinically meaningful differences in the proportion of patients with values meeting predefined limits of change criteria for any of the measured chemistry and haematology analytes. A slight mean decrease from baseline in ALT was observed with sitagliptin; from a baseline ALT value of approximately 20 IU/l in both groups, the mean changes (s.d.) from baseline of −1.3 IU/l (11.9) in the sitagliptin group compared with a slight increase of 0.9 IU/l (8.2) in the glipizide group at Week 52. A similar pattern was observed for AST, with mean changes (s.d.) from baseline at Week 52 of −0.4 IU/l (6.1) in the sitagliptin

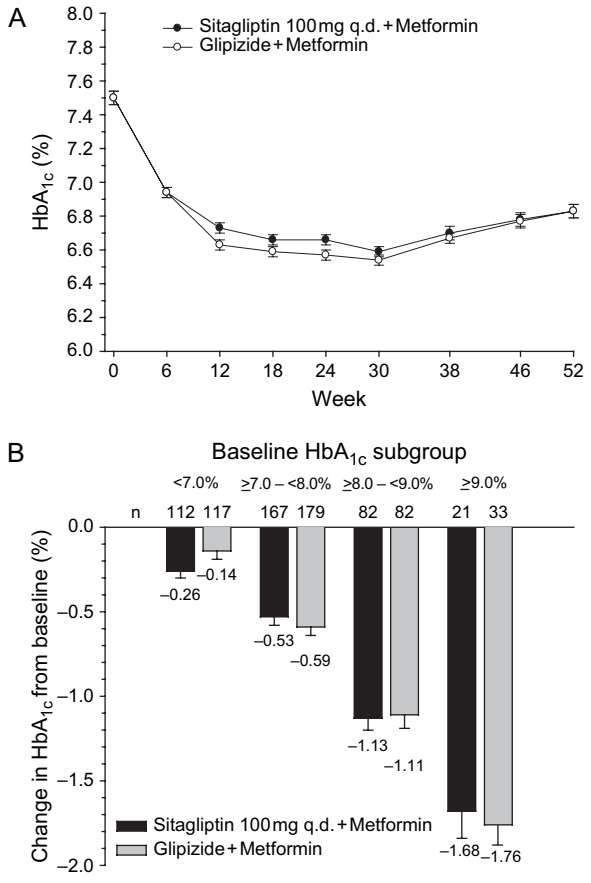

Fig. 2 (A) For the per-protocol population, haemoglobin A_{1c} (HbA_{1c}) change (±s.e.) over time in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide. (B) Mean HbA_{1c} change (±s.e.) from baseline at Week 52 by baseline HbA_{1c} subgroups.

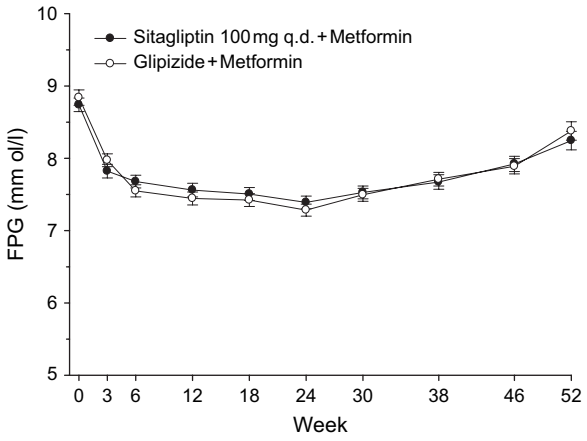

Fig. 3 For the per-protocol population, fasting plasma glucose (FPG) change (±s.e.) over time in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide.

group and 0.7 IU/l (6.3) in the glipizide group from baseline values of approximately 16 IU/l in both groups. No meaningful differences were observed in vital signs or in ECG data.

Discussion

This study provides the first add-on efficacy and safety results for sitagliptin, a DPP-4 inhibitor, compared with a standard sulfonylurea agent, glipizide, over a 52-week treatment period in patients with inadequate glycaemic control on metformin monotherapy. The study results demonstrate that sitagliptin was non-inferior to glipizide in HbA_{1c}-lowering efficacy after 52 weeks in the predefined primary analysis focusing on the PP population. Although more sitagliptin-treated patients discontinued treatment because of lack of efficacy and thus were excluded from the PP population, the APT results, which included the data from the last observation prior to discontinuation carried forward (i.e. intention-to-treat analysis), confirmed the PP results. As with most antihyperglycaemic agents, severity of hyperglycaemia at baseline notably impacted response in this study, with decreases in HbA_{1c} of 1.7% in the group of patients with baseline $HbA_{1c} \geq 9\%$. A similar proportion of patients in each group attained the HbA_{1c} targets of <7 and $<6.5\%$ after 52 weeks of treatment. In addition to similar reductions in HbA_{1c} from baseline over 52 weeks, FPG was also reduced to a similar extent in both treatment groups at Week 52.

In this study, maximal efficacy in HbA_{1c} and FPG was observed at 24 to 30 weeks, with subsequent increases in mean values of both endpoints in the sitagliptin and glipizide groups. Initial reduction in HbA_{1c} was slightly greater with glipizide than with sitagliptin ($<0.2\%$ difference), but from the nadir in HbA_{1c}, the rate of rise in the glipizide group was greater than that observed in the sitagliptin group, as assessed by the COD – the slope of the HbA_{1c} line after Week 24. Because of this more rapid deterioration with glipizide, the same extent of HbA_{1c} lowering was observed in the two groups by Week 52. An increase in FPG after the nadir was also evident in both treatment groups. Possible explanations for the rise in HbA_{1c} and FPG after nadirs were reached may include a decrease in the treatment effect because of less compliance to diet and exercise over the course of the treatment period, the natural history of the disease with progressive loss of β-cell function [24] and/or a decrease in efficacy of study drug or of metformin.

Table 3 Safety results in the all-patients-as-treated population

	Sitagliptin 100 mg q.d. + metformin (N = 588), n (%)	Glipizide + metformin (N = 584), n (%)
One or more AEs	419 (71.3)	444 (76.0)
Drug-related AEs*	85 (14.5)	177 (30.3)
SAEs	43 (7.3)	44 (7.5)
Drug-related SAEs*	0	2 (0.3)
Deaths	1 (0.2)	2 (0.3)
Discontinuations because of AEs	16 (2.7)	21 (3.6)
Discontinuations because of drug-related AEs	8 (1.4)	8 (1.4)
Discontinuations because of SAEs	6 (1.0)	7 (1.2)
Discontinuations because of drug-related SAEs	0	0
Clinical AEs of special interest		
Hypoglycaemia	29 (4.9)	187 (32.0)
Prespecified selected gastrointestinal AEs		
Abdominal pain	16 (2.7)	12 (2.1)
Nausea	15 (2.6)	16 (2.7)
Vomiting	5 (0.9)	9 (1.5)
Diarrhoea	34 (5.8)	32 (5.5)

AE, adverse experience; HbA_{1c}, haemoglobin A_{1c}, SAE, serious AE.
*Considered by the investigator as possibly, probably, or definitely related to study drug.

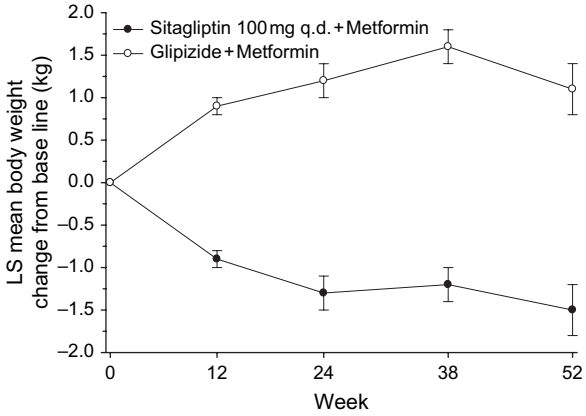

Fig. 4 For the all-patients-as-treated population, least square mean body weight change (±s.e.) from baseline over time in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide.

Several endpoints reflecting β-cell function were assessed in the study. In both treatment groups, HOMA-β increased, with a significantly greater change occurring in the glipizide group than in the sitagliptin group at Week 52. Because sulfonylurea agents directly stimulate insulin secretion, this was not unexpected. The greater increase in HOMA-β with glipizide compared with sitagliptin despite similar improvements in glycaemic control is consistent with participation of additional glucose-lowering mechanisms with sitagliptin, such as reductions in glucagon concentration [8]. The fasting proinsulin/insulin ratio is a measure of β-cell dysfunction and is typically increased in patients with type 2 diabetes [25,26]. In the present study, the proinsulin/insulin ratio increased in patients treated with glipizide but was reduced in patients receiving sitagliptin at Week 52. The deterioration in the proinsulin/insulin ratio in the glipizide group may reflect the effects of glipizide on the β-cell, through ongoing β-cell stimulation, and/or progressive β-cell deterioration [24]. The improvement in the fasting proinsulin/insulin ratio with sitagliptin suggests that this agent may have a beneficial effect on β-cell function.

In this study, both treatments were generally well tolerated. With the exception of a substantially higher rate of drug-related adverse experiences with glipizide mainly because of the increased incidence of hypoglycaemia, the overall adverse experience profiles were similar between groups. For specific adverse experiences with a higher incidence in the sitagliptin group relative to the glipizide group, the between-group difference in incidence was generally quite small, and these adverse experiences were considered generally mild or moderate in intensity and did not lead to discontinuation from the study. Indeed, no meaningful difference in adverse experiences, leading to discontinuation, or in serious adverse experiences was evident between groups, with the exception of more discontinuations because of hypoglycaemia in the glipizide group. No meaningful differences were observed in the results of laboratory safety assessments.

There was a substantial and clinically important difference in the proportion of patients reporting hypoglycaemia and in the total number of events of hypoglycaemia. Despite similar glycaemic control, 32% of patients in the glipizide group had adverse experiences of hypoglycaemia compared with 5% of patients in the sitagliptin group during this study. Importantly, patients in the glipizide group had 12 times the number of episodes of hypoglycaemia compared with patients in the sitagliptin group. A majority (73%) of these episodes had corresponding fingerstick glucose values of <3.9 mmol/l (70 mg/dl). Moreover, more patients in the glipizide group had episodes of hypoglycaemia either requiring non-medical assistance

or having characteristics of marked severity (e.g. altered mental status or requirement for medical assistance). The low incidence of hypoglycaemia with sitagliptin therapy is in agreement with the results of other clinical studies with sitagliptin in patients with type 2 diabetes [18,27,28] and is consistent with the observation that the glucose-lowering effects of incretins are glucose dependent [16].

Weight gain was also notably different between the treatment groups in this study. Over 52 weeks, patients on stable doses of metformin treated with glipizide gained weight, while those receiving sitagliptin lost weight, with a clinically meaningful between-treatment difference of 2.5 kg observed. Associated with the reduction in body weight with sitagliptin was a decrease in waist circumference, which suggests that at least part of body weight–lowering effect of sitagliptin involved a reduction in central (visceral) fat deposition. Because increases in ALT correlate with increases in hepatic fat content [29], the modest reduction in ALT with sitagliptin suggests that a decrease in hepatic fat may have occurred. Hepatic imaging would be needed to confirm this possibility. In prior studies, relative to placebo, treatment with sitagliptin has been generally shown to have a weight neutral effect in both monotherapy and as add-on to either metformin or pioglitazone [18,27,30]. However, in one 24-week monotherapy trial, weight loss relative to sitagliptin was observed in the placebo group, which likely reflected less adequate glycaemic control in the placebo group [28]. Therefore, in the context of equivalent glycaemic control to a sulfonylurea agent, the present study demonstrates that treatment with sitagliptin used in combination with metformin produces weight loss.

Glipizide was selected as a representative sulfonylurea agent in the present study because it has a similar efficacy and safety profile to that of other sulfonylurea agents [6,7]. The mean maximum dose of glipizide achieved in this study was approximately 10 mg/day. The titration of glipizide was designed to support a safe dose escalation and to avoid excessive hypoglycaemia, a concern with sulfonylurea agents. Because the study included many patients with relatively milder hyperglycaemia (~65% of patients had a baseline $HbA_{1c} < 8\%$), it was not surprising that many patients did not uptitrate to the maximum allowed dose (20 mg/day). In a dose escalation study with glipizide, near maximal efficacy was reached with a dose of 10 mg/day, with little additional efficacy obtained with dose escalation through doses of 40 mg/day [31]. Because patients in the glipizide group experienced more than 12 times as many episodes of hypoglycaemia than were reported in the sitagliptin group in this study, more aggressive titration may have led to not only a lower HbA_{1c} but also an even greater event rate of hypoglycaemia in this group.

In summary, the addition of sitagliptin compared with the addition of glipizide provided similar HbA_{1c}-lowering efficacy after 52 weeks of treatment in patients with type 2 diabetes with inadequate glycaemic control on metformin monotherapy. Although both treatments were generally well tolerated, sitagliptin had a considerably lower risk of hypoglycaemia relative to glipizide and produced weight loss compared with weight gain with glipizide.

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Conflict of Interest

Michael Nauck has received honoraria from Merck & Co. for memberships on the advisory boards and for speaking on subjects related to sitagliptin, DPP-4 inhibitors and incretins, in general. He has also received honoraria from Bristol-Myers-Squibb, GlaxoSmithKline, Merck (Darmstadt), Novartis, Probiodrug and Roche for consultations and speaking on topics closely related to sitagliptin and DPP-4 inhibitors. G. M., D. S., L. T. and P. S. are employees of Merck Research Laboratories.

Appendix 1

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