ORIGINAL PAPER

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study

T. Seck,[1] M. Nauck,[2] D. Sheng,[1] S. Sunga,[1] M. J. Davies,[1] P. P. Stein,[1] K. D. Kaufman,[1] J. M. Amatruda[1] for the Sitagliptin Study 024 Group*

[1]Merck Research Laboratories, Rahway, NJ, USA
[2]Diabeteszentrum Bad Lauterberg im Harz, Bad Lauterberg, Germany

Correspondence to:
Thomas Seck, MD
Merck Research Laboratories,
126 East Lincoln Avenue,
Mail Code: RY34-A220,
Rahway, NJ 07065-0900, USA
Tel.: 732 594 3083
Fax: 732 594 3560
Email:
thomas_seck@merck.com

*The list of study investigators was previously published in Nauck et al. (see Reference #9).

ClinicalTrials.gov:
NCT00094770 (Sitagliptin Study 024)
Clinicalstudyresults.org:
Januvia™ – Merck Protocol Number 024.

Disclosures
Michael Nauck, has received honoraria from Merck & Co., Inc. 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 other DPP-4 inhibitors.
Thomas Seck, Danielle Sheng, Sheila Sunga, Michael J. Davies, Peter Stein, Keith Kaufman and John Amatruda were employees of Merck & Co., Inc. during the conduct of this study.

SUMMARY

Objectives: To evaluate the 2-year safety and efficacy of adding sitagliptin or glipizide to ongoing metformin in patients with type 2 diabetes. **Methods:** Patients who were on a stable dose of metformin (≥ 1500 mg/day) for at least 8 weeks were randomised in a double-blind manner to receive either sitagliptin 100 mg q.d. ($N = 588$) or glipizide 5 mg/day (up-titrated up to 20 mg/day based upon prespecified glycaemic criteria) ($N = 584$). The efficacy analysis assessed the change in HbA_{1c} from baseline using the per-protocol (PP) population. **Results:** For the PP cohort, mean baseline HbA_{1c} was 7.3% in both groups. After 2 years, the least squares (LS) mean change in HbA_{1c} from baseline [95% confidence interval (CI)] was −0.54% (−0.64, −0.45) with sitagliptin ($n = 248$) and −0.51% (−0.60, −0.42) with glipizide ($n = 256$). The rise in HbA_{1c} from week 24 to week 104 [i.e. coefficient of durability (COD)] was smaller with sitagliptin [COD (95% CI) 0.16%/year (0.10, 0.21)] compared with glipizide [0.26%/year (0.21, 0.31)]. The proportion of patients with an $HbA_{1c} < 7\%$ was 63% and 59% with sitagliptin and glipizide, respectively. The beta-cell responsiveness to a meal challenge was maintained with sitagliptin and decreased with glipizide. The proportion of patients who reported hypoglycaemia was 5% with sitagliptin and 34% with glipizide [difference in proportions (95% CI) = −29% (−33, −25)]. Relative to baseline, sitagliptin was associated with weight loss (−1.6 kg) compared with weight gain (+0.7 kg) with glipizide. **Conclusion:** In patients with type 2 diabetes, adding sitagliptin to metformin monotherapy improved glycaemic control over 2 years, similar to the glucose-lowering efficacy observed with adding glipizide, but with greater durability and generally better maintenance of beta-cell function. Sitagliptin was generally well tolerated with a lower risk of hypoglycaemia and weight loss compared with weight gain observed with glipizide.

What's known
Many patients with type 2 diabetes do not achieve or maintain glycaemic goals with a single antihyperglycaemic agent and require additional therapy. Metformin is recommended as the first-line therapy for most patients with type 2 diabetes. Sulphonylureas are the most commonly prescribed second-line therapy, but are associated with weight gain and an increased risk of hypoglycaemia. Sitagliptin, a DPP-4 inhibitor, is a newer antihyperglycaemic therapy that has been shown to be weight neutral and to have a low risk of hypoglycaemia when co-administered with metformin.

What's new
The present study assessed the 2-year efficacy and safety for sitagliptin compared with glipizide, a sulphonylurea, when added to ongoing metformin therapy. After 2 years of treatment, the glucose-lowering efficacy with sitagliptin was similar to that observed with glipizide when added to ongoing metformin therapy. The addition of sitagliptin was generally well tolerated with a lower risk of hypoglycaemia, as well as, a weight loss compared with a weight gain observed with the addition of glipizide.

Introduction

Due to the progressive nature of the disease, over time, patients with type 2 diabetes often require combinations of medications to maintain glycaemic control (1). Metformin is the most commonly prescribed oral antihyperglycaemic agent for initial therapy (2–4). Incretin-based therapies (e.g. dipeptidyl peptidase-4 (DPP-4) inhibitors and analogues of glucagon-like peptide-1) are newer antihyperglycaemic agents available for the treatment of type 2 diabetes (5). In studies of up to 30 weeks, sitagliptin, a DPP-4 inhibitor, added when metformin alone did not provide adequate glycaemic control, significantly improved fasting and postprandial glucose levels and measures of beta-cell function in patients with type 2 diabetes (6–8). A previous clinical study showed that the addition of sitagliptin to ongoing metformin therapy provided similar improvement in HbA_{1c} relative to the addition of rosiglitazone (8). The previously reported results from the first year of the present study (9) showed that compared with the addition of glipizide therapy, the addition of sitagliptin to metformin provided similar glycaemic efficacy with a markedly lower incidence of hypoglycaemia and with weight loss compared with weight gain with the sulfonylurea. While the primary time point for analysis for the present study was at 1 year, the study

doi: 10.1111/j.1742-1241.2010.02353.x

continued as a randomised, double-blind, active-controlled study for an additional year. The results over the 2-year treatment period are reported herein.

Patients and methods

Patients

Patient selection criteria

The screening/eligibility criteria for this study have been previously published in detail elsewhere (9) and are summarised here. Men and women (aged 18–78 years) with type 2 diabetes who were either not taking an antihyperglycaemic agent, were taking any oral antihyperglycaemic agent as monotherapy or were taking metformin in combination with another oral antihyperglycaemic agent were eligible to participate in the study if they met all screening criteria. Patients provided written informed consent to participate. Patients received counselling on exercise and a diet consistent with American Diabetes Association recommendations throughout the study.

Study design

The study protocol (Sitagliptin Study 024; ClinicalTrials.gov NCT00094770) was reviewed and approved by the appropriate committees and authorities for each study site and performed in accordance with the Declaration of Helsinki.

The glycaemic inclusion criteria were outlined previously (9). Briefly, patients who were already on metformin ≥ 1500 mg/day for at least 10 weeks and had an HbA_{1c} ≥ 6.5% and ≤ 10% directly entered a 2-week, single-blind, placebo run-in period. Patients not on an antihyperglycaemic agent, on an oral antihyperglycaemic agent other than metformin monotherapy at a dose ≥ 1500mg/day or on metformin in combination with another oral antihyperglycaemic agent entered a metformin monotherapy treatment titration and dose-stable period of at least 6 weeks and a placebo run-in period of 2 weeks. Patients with an HbA_{1c} ≥ 6.5% and ≤ 10% after the metformin dose-stable period at the beginning of the 2-week placebo run-in period and who met all other eligibility criteria were randomised into the study, using a computer-generated allocation schedule, in a 1 : 1 ratio to double-blind treatment with the addition of sitagliptin or glipizide to ongoing metformin therapy. Patients in the sitagliptin group were treated with sitagliptin 100 mg once daily and matching glipizide placebo. Patients in the glipizide group received a matching sitagliptin placebo tablet and started glipizide with a dose of 5 mg/day. The glipizide dose was up-titrated, to a maximum dose of 20 mg/day, in three-week intervals during the first 18 weeks of treatment if all premeal fingerstick glucose values were > 6.1 mmol/l (110 mg/dl) during the week prior to the study visit. At the investigator's discretion, up-titration of glipizide was withheld if the investigator considered that up-titration would place the patient at risk for hypoglycaemia. At any time during the study, glipizide could be down-titrated to prevent recurrent hypoglycaemic events. Compliance with treatment was assessed as the proportion of study drug taken in relation to that prescribed over 2 years.

Throughout the study, patients were discontinued if they failed to meet prespecified, progressively stricter glycaemic control criteria. From randomisation through week 6, patients were discontinued for fasting plasma glucose (FPG) > 15.0 mmol/l (270 mg/dl); after week 6 through week 12, FPG > 13.3 mmol/l (240 mg/dl); after week 12 through week 18, FPG > 12.2 mmol/l (220 mg/dl); after week 18 through week 30, FPG > 11.1 mmol/l (200 mg/dl); after week 30 through week 52, HbA_{1c} > 8.0%; and after week 52 to week 104, HbA_{1c} > 7.5%.

Study evaluations

Safety assessments

Data on adverse experiences, physical examinations, vital signs (e.g. blood pressure, pulse rate), electrocardiograms (ECG) 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.

Events of hypoglycaemia were considered of special interest. Patients were counselled regarding the symptoms of hypoglycaemia (e.g. weakness, dizziness, shakiness, increased sweating, palpitations, or confusion) and requested to immediately perform a fingerstick glucose measurement if any symptoms occurred that may have been related to hypoglycaemia, but to avoid delay in treating these symptoms. To assist the investigator in assessing the severity of an event, patients were provided with, and instructed in the use of, a hypoglycaemia assessment log to document potential hypoglycaemia episodes and collect information on the severity of the events (such as the requirement for the assistance of another person or medical treatment). Events assessed by the investigator as hypoglycaemia were reported as clinical adverse experiences of hypoglycaemia; documentation of a glucose determination at the time the patient had symptoms was not required for an event to be reported as hypoglycaemia. Events of symp-

tomatic hypoglycaemia were analysed as follows: those not requiring assistance; those requiring the (non-medical) assistance of others; and those requiring medical intervention or exhibiting markedly depressed level of consciousness, including loss of consciousness or seizure.

Efficacy assessments

After an overnight fast, blood samples were collected for the assessment of HbA_{1c}, FPG, serum insulin, serum proinsulin, and plasma lipid parameters [total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C)] at baseline and at various time points during the study. Homeostasis model assessment-beta cell function (HOMA-β), proinsulin/insulin ratio, HOMA-insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated (10,11). As a prespecified analysis, durability of the two treatments was evaluated by comparing the rate of change in HbA_{1c} from week 24 to the end of the 2nd year [defined as the coefficient of durability (COD)]. For the COD analysis, week 24 was prespecified as the first time point of interest because the maximum treatment effect for both agents was expected to occur near this time. The proportion of patients with an $HbA_{1c} < 7\%$ after 2 years was determined, as well as the proportion of patients who had an $HbA_{1c} < 7\%$ at the end of both the 1st and 2nd years.

Postprandial glucose response and beta-cell function were assessed in a subset of patients who volunteered to undergo 9-point meal tolerance tests at baseline (prior to first dose of study medication) and at 2 years. The meal tolerance test at 2 years was performed 4–7 days following a blinded treatment washout period (i.e. patients were continued on placebo matching their active study medications) to assess the effects of chronic treatment on beta-cell function separated from the direct pharmacological effects of each treatment. The meal test was a mixed meal consisting of two nutrition bars and one nutrition drink (approximately 680 kcal total; 111 g of carbohydrate, 14 g of fat, and 26 g of protein). Patients were instructed to consume the entire meal within 15 min. Blood samples for the 9-point meal tolerance test were collected at the following time points for the measurement of plasma glucose and serum C-peptide and insulin: −10 min before the start of the meal, 0 (immediately prior to a meal), and 10, 20, 30, 60, 90, 120 and 180 min after the start of the meal. The same assessments were made after 1 year of treatment and following a 4- to 7-day transient washout period. After the 9-point meal tolerance test at 1 year, the patients resumed their double-blind study treatment.

Beta-cell function was assessed from glucose and C-peptide concentrations measured in the 3-h period after the meal, by using the C-peptide minimal model (12). The model assumes that insulin secretion is made up of three components: static, dynamic and basal. The static component (Φ_s) characterises the insulin secretion response to the above-basal glucose concentration. The dynamic component (Φ_d) characterises the insulin secretion response to the rate of increase of glucose. The basal component (Φ_b) is a measure of beta-cell responsiveness to glucose under basal conditions. The total responsivity index (Φ_{total}) is a pooled parameter, defined as the average insulin secretion rate above the basal level over the average glucose concentration, calculated as a function of Φ_s and Φ_d. Another parameter derived from the model is the delay time constant, T (min; the observed lag-time between a glucose stimulus and Φ_s). Insulin sensitivity was assessed using the insulin sensitivity index (ISI), an index that uses the postmeal glucose and insulin levels to characterise insulin sensitivity that correlates well with insulin sensitivity as measured by the euglycaemic insulin clamp (13). The disposition index (DI) characterises beta-cell function by examining insulin secretion in the context of insulin sensitivity. DI was determined by multiplying the Φ_{total} by the ISI.

All laboratory measurements and ECG assessments were performed at central laboratories (PPD Global Central Labs, LLC, Highland Heights, KY and Zaventem, Belgium; Covance Central Diagnostics, Inc., Reno, NV, USA) as previously described (9).

Statistical analyses

The statistical analysis plan for the year 2 analysis was written as part of the protocol and the Statistical Analysis Plan before the initial unblinding for the primary analysis of year 1 data. The primary efficacy analysis and hypothesis focused on the change from baseline in HbA_{1c} for the per-protocol (PP) population at 1 year for the sitagliptin group relative to the glipizide group using a non-inferiority approach, as previously reported (9). There were no predefined efficacy hypotheses for the 2-year results and, thus, no inferential testing at this time point was performed. For the 2-year efficacy endpoints, analyses assessed the change from baseline using the PP population. The PP cohort consisted of patients who completed the 2-year treatment period and did not have any reasons for exclusion from this cohort, including the absence of baseline data, the absence of treatment data at the end of the 2nd year, or major

protocol violations (e.g. drug compliance < 75%; change in metformin dose; addition of non-study antihyperglycaemic agents). For efficacy endpoints, an analysis of covariance (ANCOVA) model was used to compare the treatment groups, focusing on change from baseline at the end of the 2nd year, with baseline values and prior antihyperglycaemic agent status as covariates. As prespecified, the differences in least squares (LS) mean change (or percent change) from baseline to the end of the 2nd year and 95% confidence intervals (CI) were provided for the between-group comparisons. For assessment of beta-cell function, patients who underwent meal tolerance tests at both baseline and 2 years and also met the requirements for inclusion in the PP population were included in the analysis. For the analyses of the PP population, missing values were not imputed.

To support the findings in the analysis of the PP population, additional efficacy analyses were performed for key endpoints (HbA_{1c} and FPG) on the all-patients-treated (APT) cohort that consisted of all randomised patients who received at least one dose of study treatment and who had both a baseline and at least one postbaseline measurement. Missing values in the APT analysis were imputed by the last observation carried forward approach over the 2-year study.

Safety and tolerability were evaluated over the 2-year treatment period 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 (APaT) cohort, which was defined as all randomised patients who received at least one dose of study medication. Specific clinical adverse experiences of interest included hypoglycaemia and prespecified selected gastrointestinal adverse experiences (abdominal pain, nausea, vomiting, and diarrhoea). For these adverse experiences of interest, comparisons of proportions of patients were performed using Fisher's exact test; 95% CIs for the between-group differences were calculated using the modified Wilson's method (14). For body weight, an ANCOVA model was used to compare the treatment groups, focusing on change from baseline at the end of the 2nd year, with baseline values and prior antihyperglycaemic agent status as covariates. In the analyses of safety parameters, missing values were not imputed.

Results

Patient disposition and characteristics

In this study, 519 of the 1172 randomised patients (44%) completed the 2-year treatment period, of which 504 were included in the PP analysis (sitagliptin $n = 248$; glipizide $n = 256$) (Figure 1). The proportions of patients discontinuing treatment and the reasons for discontinuation were generally similar between groups, with patients discontinuing for lack of efficacy (i.e. patients not meeting the progressively stricter, protocol-specified glycaemic criteria and/or not meeting the investigator's expectations of glycaemic improvement) accounting for 52% of the discontinuations over the 2-year treatment period (Figure 1). For the randomised cohort, the baseline characteristics were generally similar between treatment groups, as previously published (9). The baseline characteristics of the patients in the 2-year PP cohort were also similar between the sitagliptin and glipizide groups (Table 1). As a result of the progressively stricter glycaemic criteria requiring discontinuation from the study, patients in the 2-year PP cohort tended to have better glycaemic control at baseline, with lower mean HbA_{1c} and FPG values and a shorter mean duration of type 2 diabetes compared with those who did not complete the 2-year treatment period (data not shown).

Over the 2-year treatment period, the mean daily dose of glipizide in the PP population was 9.2 mg per day, with approximately 66% reaching a dose of glipizide of at least 10 mg per day. At study end, 16% of the glipizide-treated patients were on a dose of 20 mg per day. Down-titration or interruption of glipizide was permitted as needed to prevent recurrent hypoglycaemia, and 10% of patients were not taking glipizide in the 2 weeks period prior to the end of the study. For the APT cohort, the mean daily dose of glipizide was 9.5 mg per day over the 2-year treatment period. For all randomised patients, the mean duration of exposure to study drug was modestly greater in the sitagliptin group [483.1 days (69.0 weeks)] compared with the glipizide group [467.0 days (66.7 weeks)]. The mean (median) compliance rates, defined as the proportion of study drug taken in relation to the prescribed study drug over 2 years, were 98.5% (99.8%) and 98.0% (99.7%) in the sitagliptin and glipizide groups respectively.

Efficacy

In the PP cohort, the addition of sitagliptin to ongoing metformin monotherapy led to similar reductions in HbA_{1c} from baseline after 2 years of treatment compared with the addition of glipizide (Table 2). In the PP cohort, the proportion of randomised patients with an $HbA_{1c} < 7\%$ at the end of the 2nd year was similar between the sitagliptin (63%; $n/N = 157/248$) and the glipizide (59%; 151/256) groups. Of those patients in the PP analysis

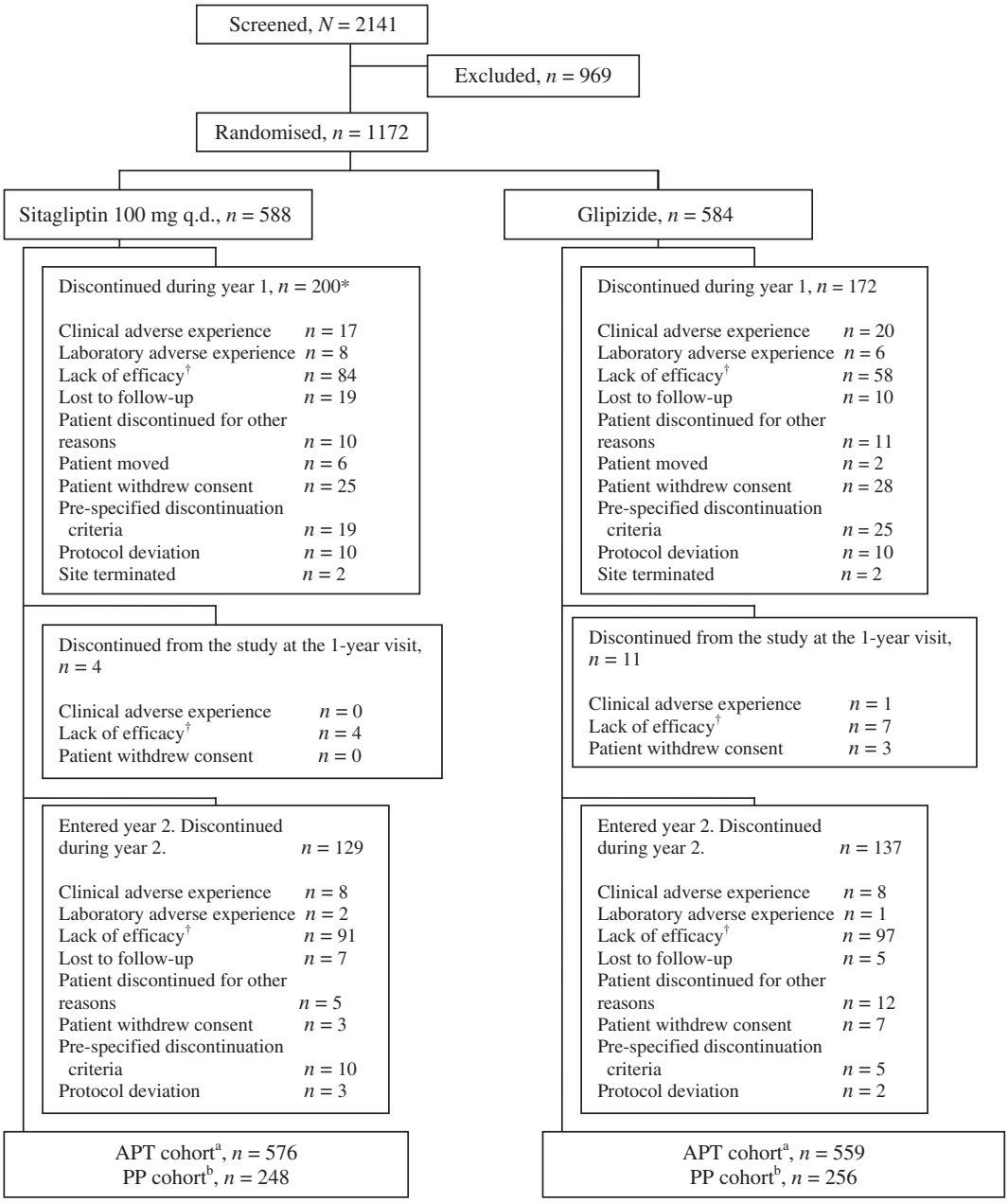

Figure 1 Patient disposition for the 2-year study. *In the sitagliptin group, the number of patients who discontinued was previously reported as 202 (Nauck et al. (9)), but was corrected to 200 during the 2nd year of the study. †Patients discontinued for lack of efficacy included patients not meeting the progressively stricter protocol-specified glycaemic criteria and/or not meeting the investigator's expectations of glycaemic improvement. [a]All-patients-treated (APT) cohort includes randomised 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 randomised patients who completed 2 years of treatment and did not have any reasons for exclusion from this cohort, including no baseline data, no treatment data at week 104, or major protocol violations.

who had an $HbA_{1c} < 7\%$ at the end of the 1st year, completed 2 years of therapy and had a HbA_{1c} measurement at year 2, 73% ($n/N = 141/193$) in the sitagliptin group and 69% (135/196) in the glipizide group had an $HbA_{1c} < 7\%$ at the end of the 2nd year.

The rise in HbA_{1c} from week 24 to the end of the 2nd year was less with sitagliptin treatment compared with glipizide [coefficient of durability (COD) (95% CI): 0.16%/year (0.10, 0.21) vs. 0.26%/year (0.21, 0.31) respectively; between-group difference in COD (95% CI) = −0.10%/year (−0.16, −0.05)] (Figure 2).

Table 1 Baseline demographics and efficacy endpoint data for the 2-year per-protocol cohort

Characteristic	Sitagliptin + Metformin (*n* = 248)	Glipizide + Metformin (*n* = 256)
Age, years	57.6 (8.5)	57.0 (9.1)
Gender, *n* (%)		
Male	142 (57.3)	161 (62.9)
Female	106 (42.7)	95 (37.1)
Race, *n* (%)		
Caucasian	192 (77.4)	201 (78.5)
Black	9 (3.6)	13 (5.1)
Hispanic	14 (5.6)	13 (5.1)
Asian	23 (9.3)	21 (8.2)
Other	10 (4.0)	8 (3.1)
Body weight, kg	88.5 (16.8)	90.3 (16.5)
Body mass index, kg/m^2	30.9 (4.8)	31.3 (5.0)
Duration of type 2 diabetes, years	5.8 (5.7)	5.7 (4.9)
Use of oral AHA at screening, *n* (%)		
Dual therapy	53 (21.4)	48 (18.8)
Monotherapy	183 (73.8)	193 (75.4)
None	12 (4.8)	15 (5.9)
HbA_{1c}, %	7.3 (0.6)	7.3 (0.7)
(Range)*	(6.1–9.3)	(5.8–9.9)
HbA_{1c} distribution at baseline, *n* (%)		
$HbA_{1c} < 7\%$	88 (35.5)	89 (34.8)
$HbA_{1c} \geq 7$ and $< 8\%$	114 (46.0)	121 (47.3)
$HbA_{1c} \geq 8$ to $< 9\%$	40 (16.1)	35 (13.7)
$HbA_{1c} \geq 9\%$	6 (2.4)	11 (4.3)
Fasting plasma glucose, mmol/l	8.4 (1.7)	8.5 (1.9)

AHA, antihyperglycaemic agent. Data are expressed as mean (± standard deviation) or frequency [*n* (%)], unless otherwise indicated. *HbA_{1c} eligibility criteria for randomisation into the study were based upon HbA_{1c} values obtained upon initiation of the 2-week single-blind placebo run-in. Baseline HbA_{1c} measurements were obtained after this run-in period (i.e. at the randomisation visit), and thus baseline HbA_{1c} values may have been outside the range specified by the eligibility criteria.

Results based on the PP cohort were supported by the results based on the APT cohort. For the APT cohort, LS mean HbA_{1c} change (95% CI) from a mean baseline of 7.69% was −0.33% [(−0.42, −0.25); $n = 576$] in the sitagliptin group and from a mean baseline of 7.65% was −0.35% [(−0.44, −0.26); $n = 559$] in the glipizide group [between-group difference (95% CI) = 0.01% (−0.08, 0.10)]. In the APT cohort at week 104, 42% and 39% of the patients had an $HbA_{1c} < 7\%$ in the sitagliptin and glipizide groups respectively. Similar between-group differences for COD were noted for the PP and APT cohorts (data not shown).

In the PP cohort for both treatments, the FPG change from baseline at the end of the 2nd year was similar between groups (Table 2 and Figure 3). For the APT cohort, the LS mean change from baseline (95% CI) in FPG was −0.6 mmol/l (−0.8, −0.3) [−10.1 mg/dl (−14.4, −5.7); $n = 581$] in the sitagliptin group and −0.6 mmol/l (−0.8, −0.3) [−10.3 mg/dl (−14.7, −6.0); $n = 566$] in the glipizide group [between-group difference (95% CI) = 0.0 mmol/l (−0.2, 0.3)].

At the end of the 2nd year for the PP cohort, fasting insulin increased from baseline in the glipizide group with no change observed in the sitagliptin group, resulting in a modest difference between groups (Table 2). A decrease from baseline in fasting proinsulin and the proinsulin/insulin ratio at the end of the 2nd year was observed in the sitagliptin group relative to the glipizide group. An increase in HOMA-β from baseline was observed with glipizide. Improvements in HOMA-IR and QUICKI were observed with sitagliptin relative to glipizide at the end of the 2nd year (Table 2), suggesting a small decrease in insulin resistance associated with sitagliptin treatment.

In the subset of patients who volunteered to undergo the 9-point meal tolerance testing, the baseline demographic and disease characteristic profiles

Table 2 Key efficacy results in the per-protocol cohort after 2 years of treatment

	n	Week 0 (Baseline) mean (SD)	Week 104 mean (SD)	LS mean change from baseline (95% CI)	Difference in LS mean change (95% CI)
HbA_{1c}, %					
Glipizide + Metformin	256	7.31 (0.74)	6.80 (0.59)	−0.51 (−0.60, −0.42)	−0.03 (−0.13,0.07)
Sitagliptin + Metformin	248	7.30 (0.64)	6.77 (0.58)	−0.54 (−0.64, −0.45)	
Fasting plasma glucose, mmol/l					
Glipizide + Metformin	251	8.5 (1.9)	7.7 (1.7)	−1.0 (−1.3, −0.7)	−0.1 (−0.4, 0.2)
Sitagliptin + Metformin	249	8.4 (1.7)	7.6 (1.7)	−1.1 (−1.4, −0.8)	
Fasting serum insulin, pmol/l					
Glipizide + Metformin	241	78.0 (50.4)	94.8 (69.0)	12.6 (4.2, 20.4)	−18.0 (−26.4, −9.0)
Sitagliptin + Metformin	237	78.6 (56.4)	76.8 (43.8)	−5.4 (−13.8, 3.0)	
Fasting serum proinsulin, pmol/l					
Glipizide + Metformin	249	22.9 (18.0)	26.5 (20.1)	2.1 (−0.7, 4.8)	−6.9 (−9.7, −4.0)
Sitagliptin + Metformin	242	23.9 (20.7)	20.0 (18.3)	−4.8 (−7.6, −2.0)	
Proinsulin/insulin ratio					
Glipizide + Metformin	240	0.31 (0.16)	0.30 (0.18)	−0.01 (−0.03, 0.02)	−0.04 (−0.07, −0.01)
Sitagliptin + Metformin	235	0.32 (0.17)	0.26 (0.16)	−0.05 (−0.08, −0.02)	
HOMA-β (%)					
Glipizide + Metformin	234	59.2 (48.2)	77.5 (107.9)	19.2 (5.7, 32.7)	−6.3 (−20.3, 7.6)
Sitagliptin + Metformin	232	59.8 (50.7)	71.2 (58.0)	12.9 (−0.7, 26.5)	
HOMA-IR					
Glipizide + Metformin	234	5.0 (3.4)	5.6 (5.1)	0.2 (−0.5, 0.9)	−1.1 (−1.8, −0.4)
Sitagliptin + Metformin	232	4.9 (3.8)	4.4 (3.2)	−0.9 (−1.6, −0.2)	
QUICKI					
Glipizide + Metformin	234	0.314 (0.033)	0.311 (0.029)	−0.001 (−0.005, 0.003)	0.008 (0.003, 0.012)
Sitagliptin + Metformin	232	0.315 (0.029)	0.319 (0.029)	0.006 (0.002, 0.010)	

SD, standard deviation; LS, least squares; CI, confidence interval.

were generally similar to those of the overall study population, and were also similar between treatment groups within this subset (data not shown). After 2 years of treatment and following a 4- to 7-day blinded (the patients received placebo matching their study drug) treatment washout period, patients in the sitagliptin treatment group had lower postprandial plasma glucose excursion (AUC) after the meal relative to baseline, with no change from baseline in glucose excursion in patients in the glipizide treatment group (Table 3, Figure 4A). Serum C-peptide and insulin 3-h AUC were numerically increased with sitagliptin compared with numerical reductions with glipizide (Table 3, Figure 4B and C). The insulin AUC to glucose AUC ratio was improved from baseline in the sitagliptin treatment group [LS mean change from baseline in ratio (95% CI) = 4.21 pmol/mmol (0.11, 8.42)], whereas the ratio was minimally changed in the glipizide treatment group [0.11 pmol/mmol (−3.89, 4.21)].

Beta-cell responsiveness to the meal challenge (performed after the 4–7 day washout period) was assessed using a standard model-based approach.

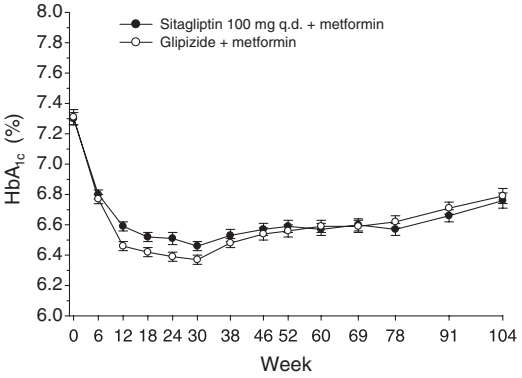

Figure 2 For the per-protocol cohort, HbA_{1c} change (LS mean ± SE) over 2 years in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide

Measures of beta-cell responsiveness postmeal (Φ_s and Φ_d) remained stable relative to baseline in patients who had been treated with sitagliptin, while a reduction in responsiveness was observed in patients who had received glipizide (Table 3). The Φ_{total}, a composite of static and dynamic beta-cell

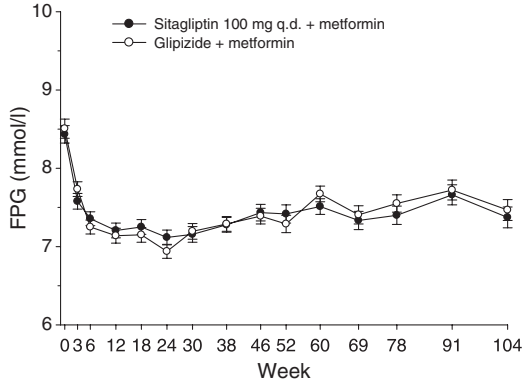

Figure 3 For the per-protocol cohort, fasting plasma glucose (FPG) change (LS mean ± SE) over 2 years in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide

responsiveness, improved from baseline with sitagliptin and remained unchanged with glipizide. The measure of basal beta-cell responsiveness (Φ_b) remained unchanged relative to baseline in both groups. DI, an assessment of beta-cell responsiveness in relation to insulin sensitivity, remained stable over 2 years with sitagliptin, but declined from baseline with glipizide (Table 3). Overall, these changes suggest that sitagliptin, compared with glipizide, led to better maintenance of beta-cell function after 2 years of treatment. Similar trends for within-group changes were observed after 1 year of treatment (data not shown).

For the PP cohort, LS mean percent changes from baseline in TC were 4.2% and 0.2% with sitagliptin and glipizide respectively [between-group difference (95% CI) = 4.0% (1.1, 6.9)] from a mean baseline of approximately 4.5 mmol/l. For LDL-C, LS mean percent changes from baseline were 7.4% and −1.0% with sitagliptin and glipizide respectively [between-group difference (95% CI) = 8.4% (2.5, 14.3)] from a mean baseline of approximately 2.5 mmol/l. For HDL-C, LS mean percent changes from baseline were 4.4% and 1.3% with sitagliptin and glipizide respectively [between-group difference (95% CI) = 3.1% (0.7, 5.4)] from a mean baseline of approximately 1.2 mmol/l. For TG, LS mean percent changes from baseline were 9.2% and 11.8% with sitagliptin and glipizide respectively [between-group difference (95% CI) = −2.7% (−11.2, 5.8)].

Safety and tolerability

Over 2 years of treatment, the incidence of clinical adverse experiences overall was lower in the sitagliptin group compared with the glipizide group (Table 4). The proportion of patients experiencing drug-related clinical adverse experiences was also lower with sitagliptin compared with glipizide. These differences were related primarily to the higher incidence of hypoglycaemia in the glipizide group. Nine deaths occurred over the 2-year treatment period: eight in the glipizide group [sudden cardiac death, myocardial infarction (n = 2), cancer-related deaths (n = 3), sepsis and a suicide that occurred 41 days following discontinuation of study drug] and one in the sitagliptin group (trauma related to being struck by a motor vehicle) (Table 4). None of the deaths was considered by the investigator as related to study drug.

The incidences of serious clinical adverse experiences were similar between treatment groups. For serious adverse experiences that were considered by the investigator to be related to study drug, there were three in the glipizide group (myocardial infarction, spontaneous abortion, and hydronephrosis) and one in the sitagliptin group (thrombocytopenia). The patient with thrombocytopenia experienced this event on day 407 and discontinued treatment with sitagliptin on day 409. A couple of days prior to the event the patient took nimesulide for headache. The investigator believed that thrombocytopenia was probably related to nimesulide; however, the investigator could not exclude study medication as a cause for the event and reported the adverse experience as possibly related to study medication. The platelet count improved upon initiation of corticosteroid therapy, with resolution of the event by day 446. The proportions of patients who discontinued because of adverse experiences were similar between treatment groups (Table 4).

Over the 2 years, there was a higher incidence (defined as between-group difference in incidence ≥ 1%) for 13 specific clinical adverse experiences in the sitagliptin group and 10 specific clinical adverse experiences for the glipizide group (Table 5). Of the adverse experiences with a higher incidence in the sitagliptin group, the 95% CI around the between-group difference in incidence excluded zero for cystitis, urinary tract infection, weight decrease, pain in extremity and asthma. Overall, the pattern of the adverse experiences (i.e. intensity, onset/duration, duration, etc.) of urinary tract infection and cystitis were similar in both treatment groups and most cases were assessed as mild or moderate in intensity and did not result in discontinuation. The mean duration of urinary tract infection and cystitis were similar in both groups and recurrence of events was uncommon. The related adverse experience of pyelonephritis was uncommon over the 2-year treatment period, reported in three patients in the glipizide group and one patient in the sitagliptin group. The overall incidence of infection-related adverse experiences was similar in the two treatment groups.

Table 3 Baseline and study endpoint results for indices of beta-cell function and insulin sensitivity from the 9-point meal tolerance tests administered following a 4- to 7-day washoff of study drug after 2 years of treatment with sitagliptin or glipizide added to ongoing metformin therapy (per-protocol cohort)

Treatment	*n*	Baseline mean ± SD	Study endpoint mean ± SD	Mean change from baseline (95% CI)
3-h Glucose AUC (mmol·h/l)				
Glipizide + Metformin	94	38.2 ± 7.88	38.3 ± 9.44	−1.40 (−3.46, 0.66)*
Sitagliptin + Metformin	81	37.3 ± 7.51	36.3 ± 7.34	−2.77 (−4.81, −0.73)*
3-h Insulin AUC (pmol·hr/l)				
Glipizide + Metformin	80	968 ± 605	1025 ± 655	−39 (−170, 93)*
Sitagliptin + Metformin	69	1219 ± 972	1290 ± 781	47 (−86, 182)*
3-h C-peptide AUC (nmol·hr/l)				
Glipizide + Metformin	93	6.6 ± 2.3	6.5 ± 2.5	−0.17 (−0.63, 0.30)*
Sitagliptin + Metformin	81	7.3 ± 2.5	7.6 ± 2.8	0.33 (−0.13, 0.79)*
HOMA-β (%)				
Glipizide + Metformin	99	53.3 ± 37.4	58.2 ± 36.6	5.0 (−0.4, 10.3)
Sitagliptin + Metformin	90	60.4 ± 48.8	67.7 ± 56.1	7.3 (0.7, 14.0)
Insulinogenic index (pmol/mmol)				
Glipizide + Metformin	83	90 ± 203	67 ± 103	−22 (−76, 32)
Sitagliptin + Metformin	79	57 ± 449	67 ± 46	9 (−97, 108)
Static beta cell sensitivity to glucose index (Φ_s) (10^{-9}/min)				
Glipizide + Metformin	81	28.5 ± 20.3	23.5 ± 14.5	−5.1 (−8.9, −1.2)
Sitagliptin + Metformin	70	29.5 ± 19.1	32.1 ± 19.1	2.6 (−2.3, 7.5)
Dynamic beta cell sensitivity to glucose index (Φ_d) (10^{-9})				
Glipizide + Metformin	82	501.3 ± 365.5	425.5 ± 264.2	−75.8 (−148.7, −3.0)
Sitagliptin + Metformin	69	521.5 ± 468.3	470.5 ± 282.4	−51.0 (−162.8, 60.9)
Total beta cell sensitivity to glucose index (Φ_{total}) (10^{-9}/min)				
Glipizide + Metformin	81	11.3 ± 5.0	10.6 ± 4.4	−0.7 (−1.5, 0.1)
Sitagliptin + Metformin	68	12.0 ± 4.2	13.2 ± 5.1	1.1 (0.3, 1.9)
Basal beta cell sensitivity to glucose index (Φ_b) (10^{-9}/min)				
Glipizide + Metformin	91	6.2 ± 3.0	6.7 ± 3.3	0.5 (0.0, 1.0)
Sitagliptin + Metformin	76	6.8 ± 3.3	7.6 ± 3.4	0.8 (0.3, 1.3)
Insulin sensitivity index (ISI)				
Glipizide + Metformin	77	3.5 ± 2.3	3.2 ± 2.1	−0.3 (−0.6, 0.0)
Sitagliptin + Metformin	65	3.3 ± 2.1	3.2 ± 1.9	−0.1 (−0.5, 0.3)
Disposition index (DI)				
Glipizide + Metformin	69	35.1 ± 21.6	29.2 ± 15.8	−5.9 (−10.4, −1.4)
Sitagliptin + Metformin	60	34.1 ± 16.9	38.0 ± 20.6	3.9 (−1.3, 9.0)
Delay between static phase insulin secretion and glucose concentration (T) (min)				
Glipizide + Metformin	78	29.4 ± 39.6	21.4 ± 14.2	−8.0 (−16.8, 0.8)
Sitagliptin + Metformin	69	25.0 ± 16.1	24.1 ± 17.0	−0.9 (−5.3, 3.6)

SD, standard deviation; CI, confidence interval.
*LS mean change from baseline (95% CI).

Of the adverse experiences with a higher incidence in the glipizide group, the 95% CI around the between-group difference in incidence excluded zero for cataract, toothache, hypoglycaemia and hypoaesthesia (Table 5). With the exception of hypoglycaemia, these adverse experiences (occurring in either group) were generally rated as mild in intensity, not considered related to study drug, and resolved while patients continued on study drug.

The incidences of gastrointestinal events overall and of the prespecified gastrointestinal events, abdominal pain, diarrhoea, nausea, and vomiting, were similar in the sitagliptin and glipizide groups.

There were 199 (34.1%) glipizide-treated patients for whom 805 episodes of hypoglycaemia were reported compared with 31 (5.3%) sitagliptin-treated patients for whom 57 episodes of hypoglycaemia were reported over the 2-year treatment period

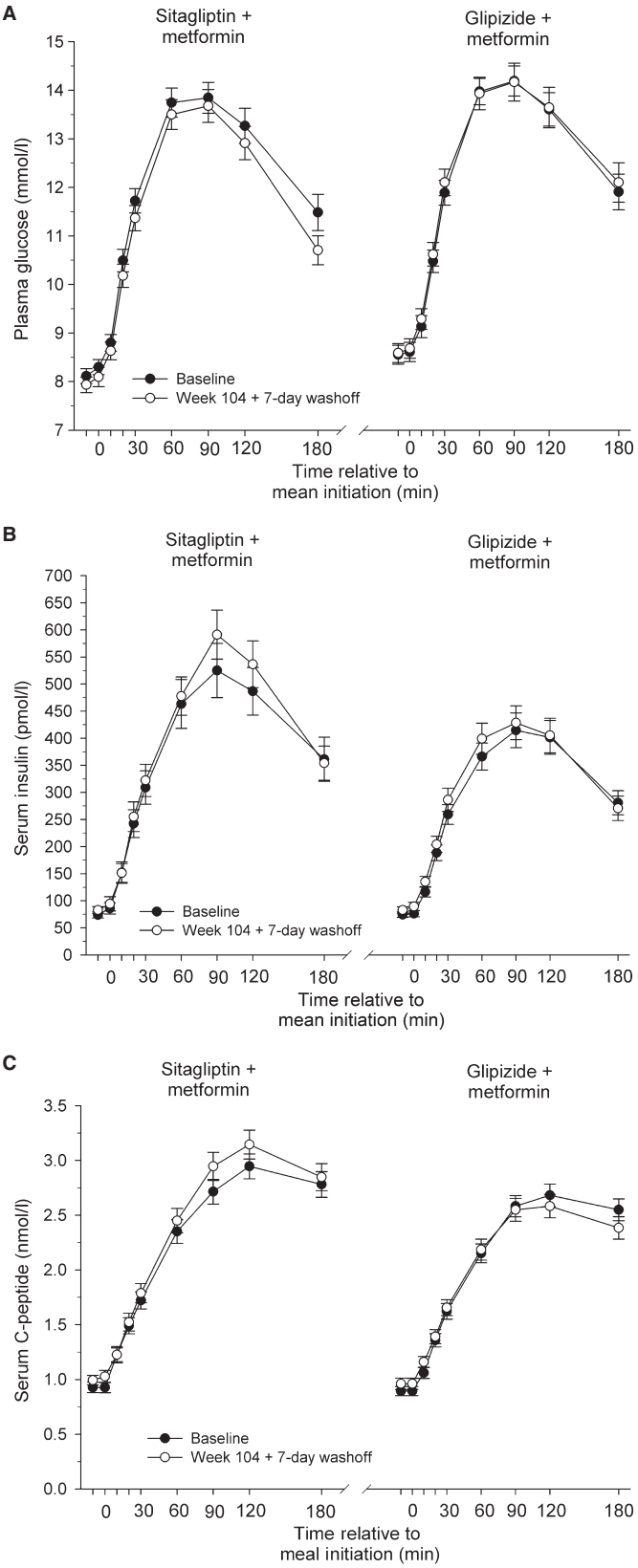

Figure 4 Plasma glucose (A), serum insulin (B), and serum C-peptide (C) profiles during the nine-point meal tolerance test at baseline and following a 4- to 7-day washoff of study drug following 2 years of treatment with sitagliptin or glipizide added to ongoing metformin therapy (mean ± SE)

Table 4 Summary of clinical adverse experiences for the all-patients-as-treated cohort over the 2-year treatment period

	Sitagliptin + Metformin (*n* = 588) *n* (%)	Glipizide + Metformin (*n* = 584) *n* (%)	Difference: Sitagliptin vs. Glipizide % (95% CI)*
One or more AEs	452 (76.9)	480 (82.2)	−5.3 (−9.9, −0.7)
Drug-related AEs†	97 (16.5)	193 (33.0)	−16.6 (−21.4, −11.7)
Serious AEs (SAEs)	64 (10.9)	73 (12.5)	−1.6 (−5.3, 2.1)
Drug-related SAEs†	1 (0.2)	3 (0.5)	−0.3 (−1.3, 0.5)
Deaths	1 (0.2)	8 (1.4)‡	−1.2 (−2.5, −0.2)
Discontinuations due to AEs	23 (3.9)	29 (5.0)	−1.1 (−3.5, 1.3)
Discontinuations due to drug-related AEs	9 (1.5)	9 (1.5)	−0.0 (−1.6, 1.5)
Discontinuations due to SAEs	10 (1.7)	14 (2.4)	−0.7 (−2.5, 1.0)
Discontinuation due to drug-related SAEs	1 (0.2)	1 (0.2)	−0.0 (−0.8, 0.8)

AE, adverse experience.
*Positive differences indicate that the proportion for the sitagliptin group is higher than the proportion for the glipizide group.
†Considered by the investigator as possibly, probably, or definitely related to study drug. ‡Includes one suicide death occurring 41 days following discontinuation from study.

Table 5 Specific clinical adverse experiences with a higher incidence in one group vs. the other and a between-treatment difference in incidence ≥ 1% for the all patients as treated cohort over the 2-year treatment period

Adverse experience	Sitagliptin + Metformin (*N* = 588) *n* (%)	Glipizide + Metformin (*N* = 584) *n* (%)	Difference: Sitagliptin vs. Glipizide % (95% CI)*
Sitagliptin > Glipizide			
Fatigue	18 (3.1)	11 (1.9)	1.2 (−0.7, 3.1)
Non-cardiac chest pain	11 (1.9)	4 (0.7)	1.2 (−0.2, 2.7)
Cystitis	8 (1.4)	1 (0.2)	1.2 (0.2, 2.5)
Nasopharyngitis	71 (12.1)	61 (10.4)	1.6 (−2.0, 5.3)
Sinusitis	26 (4.4)	18 (3.1)	1.3 (−0.9, 3.6)
Urinary tract infection	44 (7.5)	25 (4.3)	3.2 (0.5, 6.0)
Weight decreased	6 (1.0)	0 (0.0)	1.0 (0.2, 2.2)
Osteoarthritis	18 (3.1)	8 (1.4)	1.7 (−0.0, 3.5)
Pain in extremity	21 (3.6)	9 (1.5)	2.0 (0.2, 4.0)
Dizziness	26 (4.4)	19 (3.3)	1.2 (−1.1, 3.5)
Sciatica	9 (1.5)	3 (0.5)	1.0 (−0.2, 2.4)
Asthma	9 (1.5)	2 (0.3)	1.2 (0.0, 2.6)
Contact dermatitis	9 (1.5)	3 (0.5)	1.0 (−0.2, 2.4)
Glipizide > Sitagliptin			
Cataract	3 (0.5)	14 (2.4)	−1.9 (−3.5, −0.5)
Dyspepsia	11 (1.9)	20 (3.4)	−1.6 (−3.5, 0.3)
Toothache	2 (0.3)	12 (2.1)	−1.7 (−3.2, −0.5)
Peripheral oedema	13 (2.2)	22 (3.8)	−1.6 (−3.6, 0.4)
Upper respiratory tract infection	73 (12.4)	79 (13.5)	−1.1 (−5.0, 2.7)
Blood glucose decreased	3 (0.5)	16 (2.7)	−2.2 (−3.9, −0.8)
Hypoglycaemia	31 (5.3)	199 (34.1)	−28.8 (−33.0, −24.5)
Hypoaesthesia	1 (0.2)	10 (1.7)	−1.5 (−3.0, −0.4)
Prostatitis	1 (0.2)	7 (1.2)	−1.0 (−2.3, −0.0)
Cough	23 (3.9)	32 (5.5)	−1.6 (−4.1, 0.9)

CI, confidence interval.
*Positive differences indicate that the proportion for the sitagliptin group is higher than the proportion for the glipizide group. '0.0' and '−0.0' represent rounding for values that are slightly greater and slightly less than zero, respectively.

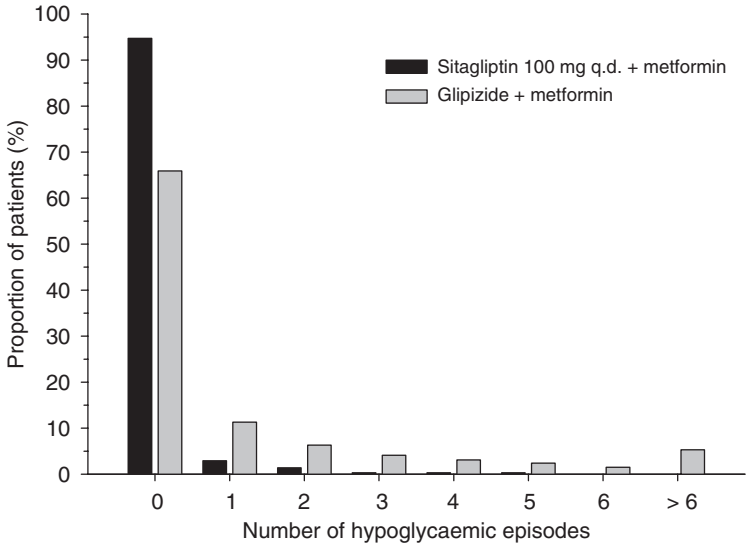

Figure 5 Proportion of patients with 0, 1, 2, 3, 4, 5, 6, or more than 6 hypoglycaemic episodes in the sitagliptin group (black bars) and glipizide group (grey bars) during the 2-year study

(Table 5). In addition to a substantially greater proportion of patients with one or more events of hypoglycaemia in the glipizide group relative to the sitagliptin group, the frequency of events among patients who had hypoglycaemia was also higher with glipizide treatment (Figure 5). Of the 726 episodes with concurrent fingerstick glucose values in the glipizide group, 554 (76%) were < 3.9 mmol/l (70 mg/dl), 242 (44%) were < 3.3 mmol/l (60 mg/dl) and 61 (8%) were < 2.8 mmol/l (50 mg/dl). Of the 49 episodes with concurrent fingerstick glucose values in the sitagliptin group, 35 (71%) were < 3.9 mmol/l (70 mg/dl), 14 (29%) were < 3.3 mmol/l (60 mg/dl), and 4 (8%) were < 2.8 mmol/l (50 mg/dl). During the first year, 83% of the 805 episodes of hypoglycaemia in the glipizide group and 88% of the 57 episodes of hypoglycaemia in the sitagliptin group occurred. Of the patients who experienced hypoglycaemic episodes, 18 and 2 patients required assistance in the glipizide and sitagliptin groups, respectively. Nine patients (1.5%) in the glipizide group had an episode that required medical assistance or exhibited markedly depressed level of consciousness compared with one patient (0.2%) in the sitagliptin group. Furthermore, nine patients (1.5%) on glipizide had a hypoglycaemic episode that required non-medical assistance compared with one patient (0.2%) on sitagliptin.

No meaningful between-group differences were observed for change from baseline in vital signs or ECG data. The addition of sitagliptin to metformin over the 2-year treatment period was associated with a reduction in body weight relative to baseline [LS mean change from baseline (95% CI) = −1.6 kg (−2.3, −1.0)], whereas the addition of glipizide increased body weight [0.7 kg (0.0, 1.3)]. The different pattern of body weight change led to a between-group difference of −2.3 kg (−3.0, −1.6) (Figure 6).

The proportions of patients for whom a laboratory adverse experience was reported were similar between groups (14.5% for sitagliptin and 12.8% for glipizide). There were no clinically meaningful differences between groups in the proportion of patients with values meeting predefined limits of change criteria for any specific chemistry or haematology analyte, including hepatic transaminases.

Discussion

In this 2-year study, the safety and efficacy of adding the DPP-4 inhibitor, sitagliptin, were compared with the safety and efficacy of adding a sulphonylurea agent, glipizide, to ongoing metformin monotherapy. At study end, sitagliptin and glipizide provided similar glycaemic control (i.e. reductions in HbA_{1c} and FPG) when added to metformin. However, the addition of sitagliptin was associated with weight loss, whereas glipizide was associated with weight gain. Furthermore, treatment with glipizide was associated with a 14-fold higher number of hypoglycaemic episodes relative to sitagliptin-treated patients over the 2-year study.

The mean dose of glipizide achieved in the present study was approximately 10 mg/day although titration to 20 mg/day was allowed during the first 18 weeks of the study. Based on previously reported results for glipizide (15), maximal or near maximal

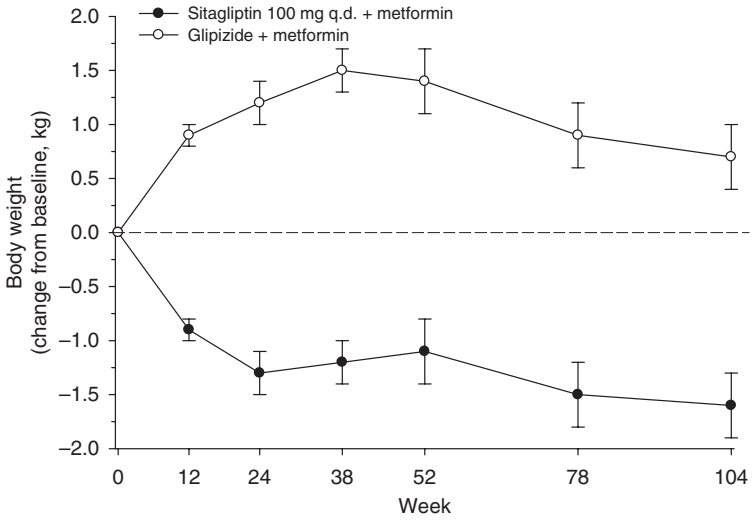

Figure 6 For the all-patients-as-treated cohort, body weight change (LS mean change from baseline ± SE) over 2 years in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide

glycaemic efficacy is achieved with a dose of 10 mg/day. This finding suggests that had the mean glipizide dose been higher, there would have been limited additional benefits on glycaemic control.

Both treatments were generally well tolerated over 2 years of treatment. Overall clinical adverse experiences and drug-related adverse experiences were observed more often with glipizide, largely related to an increased incidence of hypoglycaemia. The number of serious adverse experiences was similar in both treatment groups and no specific pattern of serious adverse experiences was observed in either treatment group. For specific adverse experiences, a few adverse experiences were more common in the sitagliptin group relative to the glipizide group and vice-versa, but these between-group differences in incidence (except for hypoglycaemia) were small. An analysis of the broader safety experience with sitagliptin did not show meaningful differences in the incidences of asthma, urinary tract infection and cystitis between sitagliptin exposed patients and patients not exposed to sitagliptin (16).

As previously stated, the proportion of patients in whom hypoglycaemia was reported as well as the total number of reported hypoglycaemic episodes were substantially higher with glipizide compared sitagliptin treatment. The majority of these episodes in the glipizide group had corresponding fingerstick glucose values of < 3.9 mmol/l (70 mg/dl) and almost half had corresponding fingerstick glucose values of < 3.3 mmol/l (60 mg/dl). In addition, more glipizide-treated patients had episodes that required assistance and/or were of marked severity. Although most hypoglycaemic episodes overall occurred in the first year of this study, patients in the glipizide group were also reported to have substantially more episodes in the second year compared with patients in the sitagliptin group.

As add-on treatment to metformin, after 2-years, the glucose-lowering efficacy with sitagliptin and glipizide was similar. The HbA_{1c} and FPG results at 2-years in the present report are consistent with the previously published results from the first year of the study (9). These changes in HbA_{1c} enabled approximately 60% of patients in the PP cohort to have an $HbA_{1c} < 7\%$ at study end. Nearly three-quarters of patients on sitagliptin in the 2-year PP cohort with an $HbA_{1c} < 7\%$ at week 52 also had an $HbA_{1c} < 7\%$ at week 104. As less than half of the randomised population was included in the PP analyses at 2 years, an APT analysis was performed and the results were consistent with and supported the HbA_{1c} and FPG results from the PP analyses. The durability of treatment effects, assessed by the prespecified analysis of COD values, was greater in the sitagliptin group compared with the glipizide group.

Measures of beta-cell function and insulin resistance/sensitivity were assessed in this study. The fasting proinsulin/insulin ratio, considered a measure of dysfunction or stress on the beta cell, was improved in patients on sitagliptin relative to those on glipizide. HOMA-β was increased in the glipizide group with a trend towards an increase in the sitagliptin group at the end of the 2nd year of the study, reflective of the ability of both agents to stimulate the secretion of insulin from the beta cell.

In a subset of patients, beta-cell responsiveness was evaluated in response to a mixed meal tolerance test. To separate the chronic effects of each treatment on beta-cell function from its direct pharmacologic

effects, beta-cell function was assessed following a 4- to 7-day treatment washout period after the 2 years of treatment, using the C-peptide minimal model. After washout of study drug, patients who had received sitagliptin over the 2-year period had lower postprandial plasma glucose excursion following the mixed meal relative to baseline, suggesting a residual beneficial effect of the drug. In comparison, patients who had received glipizide had no evident residual effect of drug, with no change from baseline in glucose excursion.

The improved glucose excursion after the meal described above was associated with improved post-meal beta-cell responsiveness. Model-based parameters of beta-cell function were stable or improved with sitagliptin, whereas most of these parameters deteriorated in patients who had received glipizide. Although similar populations were included in this analysis, the results may be limited by the small sample size of the patients who participated in the meal tolerance test. Pancreatic alpha-cell function was not assessed in this study. Alpha-cell function is altered in patients with type 2 diabetes (17), and is improved with sitagliptin treatment (18). Hence, it could also have played a role in the improvements in glucose excursion that were observed with sitagliptin. As declining beta-cell function is the major determinant for the deterioration in glycaemic control in patients with type 2 diabetes (19,20), these present data suggest a potentially beneficial effect of long-term treatment with the addition of sitagliptin to ongoing metformin therapy on glycaemic control and beta-cell function in patients with type 2 diabetes.

Insulin resistance or sensitivity, assessed with HOMA-IR and QUICKI, respectively, showed small improvements in sitagliptin-treated patients compared with no change from baseline in glipizide-treated patients. This observation could be at least partially related to the decrease in body weight in the sitagliptin group and the increase in body weight observed for the glipizide group over the 2-year treatment period. Collectively, the improvements in beta-cell function and insulin resistance with the addition of sitagliptin to metformin may contribute to the greater durability of efficacy with this combination observed in this 2-year study.

As most patients with type 2 diabetes are overweight or obese, an increase in body weight is an undesired side effect associated with certain anti-hyperglycaemic agents (21). In this study, the pattern of body weight change was different between groups over the 2-year treatment period. The addition of sitagliptin to ongoing metformin monotherapy was associated with weight loss compared with the weight gain associated with the addition of glipizide, resulting in a clinically meaningful between-treatment difference of 2.3 kg at the end of 2 years. The weight loss observed in the sitagliptin group after 1 year of treatment was maintained over the second year of the study and supports the previous conclusion that in the context of similar glycaemic control, the addition of sitagliptin to ongoing metformin monotherapy is associated with a reduction in body weight (9). In agreement with this finding, results from shorter-term studies of the addition of sitagliptin to ongoing metformin therapy have demonstrated small (~0.5 kg) reductions from baseline in body weight (6–8).

No meaningful between-group differences were observed in the results of laboratory safety assessments, including hepatic enzymes. After 2 years of treatment, slight increases in TC, LDL-C and HDL-C were observed with sitagliptin compared with glipizide. The between-group changes for TC and LDL-C are not consistent with previous 1-year results from this study (9), where no significant differences between the sitagliptin group and the glipizide group were observed for both lipid parameters. Moreover, in placebo-controlled trials, the addition of sitagliptin to ongoing metformin generally resulted in neutral or small beneficial effects relative to placebo on the lipid profile (6–8).

In summary, the addition of sitagliptin to ongoing metformin monotherapy provided similar HbA_{1c}-lowering efficacy after 2 years of treatment compared with the addition of glipizide. Durability (defined as the slope of change in HbA_{1c} over time) and beta-cell function assessed in a subset of patients after a brief washout of blinded therapy were greater with sitagliptin, suggesting a more durable glycaemic response for sitagliptin-treated patients. Patients treated with sitagliptin compared with those treated with glipizide had a lower incidence of hypoglycaemia and experienced weight loss vs. weight gain.

Acknowledgements

This study was funded by Merck & Co., Inc., Whitehouse Station, NJ. The Merck employees, who are authors, developed the study design, collected and analysed the data and prepared and approved the manuscript.

Author Contributions

Concept/design: PPS, KDK, JMA; Data collection/analysis/interpretation: TS, MN, DS, SS, MJD, PPS, KDK, JMA; Drafting manuscript: TS, MJD; Critical revision: MN, DS, SS, PPS, KDK, JMA;

Approval of manuscript: TS, MN, DS, SS, MJD, PPS, KDK, JMA.

References

1 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; **281**: 2005–12.

2 Doro P, Benko R, Kosik E, Matuz M, Toth K, Soos G. Utilization of oral antihyperglycemic drugs over a 7-year period (1998-2004) in a Hungarian population and adherence to drug therapy. *Eur J Clin Pharmacol* 2005; **61**: 893–7.

3 Lub R, Denig P, van den Berg PB, Hoogenberg K, de Jong-van den Berg LT. The impact of new insights and revised practice guidelines on prescribing drugs in the treatment of type 2 diabetes mellitus. *Br J Clin Pharmacol* 2006; **62**: 660–5.

4 Patel H, Srishanmuganathan J, Car J, Majeed A. Trends in the prescription and cost of diabetic medications and monitoring equipment in England 1991-2004. *J Public Health (Oxf)* 2007; **29**: 48–52.

5 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368**: 1696–705.

6 Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; **29**: 2638–43.

7 Raz I, Chen Y, Wu M et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin* 2008; **24**: 537–50.

8 Scott R, Loeys T, Davies MJ, Engel SS. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2008; **10**: 959–69.

9 Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. 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. *Diabetes Obes Metab* 2007; **9**: 194–205.

10 Katz A, Nambi SS, Mather K et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000; **85**: 2402–10.

11 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–9.

12 Breda E, Cobelli C. Insulin secretion rate during glucose stimuli: alternative analyses of C-peptide data. *Ann Biomed Eng* 2001; **29**: 692–700.

13 Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; **22**: 1462–70.

14 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998; **17**: 873–90.

15 Stenman S, Melander A, Groop PH, Groop LC. What is the benefit of increasing the sulfonylurea dose? *Ann Intern Med* 1993; **118**: 169–72.

16 Williams-Herman D, Round E, Swern AS et al. Safety and tolerability of sitagliptin in patients with type 2 diabetes: a pooled analysis. *BMC Endocr Disord* 2008; **8**: 14.

17 Dunning BE, Gerich JE. The role of alpha-cell dysregulation in fasting and postprandial hyperglycemia in type 2 diabetes and therapeutic implications. *Endocr Rev* 2007; **28**: 253–83.

18 Herman GA, Bergman A, Stevens C et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2006; **91**: 4612–9.

19 DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am* 2004; **88**: 787–835.

20 Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003; **46**: 3–19.

21 Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 2002; **287**: 360–72.

Paper received December 2009, accepted January 2010